EFFECTS OF MEDICAL AND SOCIAL PRACTICES ON THE FREQUENCY OF DELETERIOUS GENES IN THE POPULATION

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CONTENTS

SUMMARY

Since the virtual eradication of many infectious diseases in civilised populations, diseases which are at least partially genetic have increased in their importance as the primary cause of death and morbidity. Much concern has been expressed that current and future medical practices might further increase the burden on medical services of genetic diseases by causing increases in their incidence. In this thesis a study has been made of eugenic, as well as dysgenic, effects of some of these possible practices.

Single generation changes in disease incidence and gene frequency have been calculated for practices acting alone and in combination. No attempt has been made to calculate possible effects of changes in existing forces such as mutation and natural selection. All the changes calculated are those which would result from the new practices acting alone and this makes it possible to measure the relative effects of the new forces.

Formulae for calculating possible changes have been derived for AR, AD, XR and MF diseases and graphs drawn to illustrate the effects of the practices for diseases of early onset where affected individuals have low fitness. The theoretical changes calculated suggest that with the possible exception of AD diseases and AR diseases where there is heterozygote advantage the overall effect of the practices is likely to be a decrease in disease incidence in one generation. The estimated changes in gene frequency indicate that there is likely to be a longer term decrease in incidence of AR diseases but there might be an increase in incidence of AD and XR diseases.

The realisation of these theoretical changes is dependent upon the feasibility of the practices for particular diseases, the proportion of individuals ascertained and the proportion of these individuals adopting a particular practice. At present the practices are only possible for a limited number of diseases but prospects seem hopeful for their extension to other diseases particularly those with AR and XR modes of inheritance. Most individuals to whom the practices would be relevant are only ascertained at a stage when their subsequent adoption of any of the practices would have a minimal effect on the overall disease incidence. There is much scope for detecting more individuals at risk by contacting relatives in families with AD and XR diseases or by screening to detect heterozygous carriers in recessive diseases. The results of the follow-up studies discussed in section (3) indicate that couples would use the new practices if they were available.

Thus it seems that with advances in medical research and the detection of more individuals at risk these theoretical changes might actually occur. However in many cases the changes might be limited by some of the factors discussed in section (10) particularly cost and availability of resources.

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(1) INTRODUCTION

Genetic diseases have increased in relative importance in recent years both as a cause of death and as a cause of morbidity. The development of treatments for many infectious diseases by the introduction of new drugs and the improvement in living conditions have resulted in a sharp decline in infant mortality. Genetic diseases, which are far less amenable to treatments of this kind have increased in their relative importance as a cause of childhood death. It is also likely that many older people, now affected by genetic diseases, would have died in earlier times from infectious diseases, before the genetic disease produced recognisable symptoms.

Gordon (1971) reports that the total infant mortality rate in the U.S.A. has fallen from 101 to 25 per 1000 live births between 1916 and 1965. He also calculates that in 1910 there were six infant deaths from diarrheal diseases (enteritis, colitis and dysentry) for every death from congenital malformations. Now the reverse is true. Carter (1956) examined the causes of deaths of children having post mortem examinations in London hospitals between 1914 and 1954. In 1914 only 16 per cent of deaths could be attributed to genetic or partly genetic causes and over 68 per cent were primarily non genetic. The other deaths were due to diseases of unknown causation. About half the children in this group died from neoplasms. In 1954 38 per cent were due wholly or partly to genetic causation and only 15 per cent were non genetic. The latter result is similar to that obtained by Roberts, Chavez and Court (1970) in a study of the causes of death of 1041 children in Newcastle hospitals between 1960 and 1966 in which they found that genetically determined disease

contributed 42 per cent of the total mortality in childhood.

The great majority of genetic diseases are rare, most having frequencies of much less than 1 in 1000 live births. Although each one is rare there are a large number of them. McKusick (1971) has catalogued 1876 genetic disorders and traits which could show Mendelian inheritance and there are many diseases which are at least partly genetic. Stevenson (1961) has estimated that some five per cent of all live born children have some defect which is partially or wholly genetically determined. This figure includes 2.5 per cent of children with some macroscopic abnormality (2 per cent partially genetic and 0.5 per cent due to a single gene substitution) and 0.8 per cent who will develop a disease after birth due to a single gene trait. Taking the figure of five per cent of children with some defect, in combination with the estimate of Roberts et al (1970), would suggest that these children are about eight times more likely to die in childhood than normal children.

Genetic disease imposes a burden on society because of the necessity for expensive, often long drawn out, episodes of treatment, which may require institutionalisation. Stevenson (1959) has made rough estimates of the call on medical services in Northern Ireland by persons suffering from genetic diseases. Excluding mental illnesses such as schizophrenia, these persons are responsible for about three per cent of consultations with general practitioners, seven per cent of consultations with specialists and occupy about five per cent of hospital beds.

There are specific burdens imposed upon the family of a child with a genetic disease, in additional to the problem of management of a

chronically sick child. Murphy (1969) defines 'burden' as 'the total amount of distress that an affected child engenders'. This will depend upon the age of onset of the disease, its severity and its duration. Tips and Lynch (1963) studied adult kindred members of families into which children with genetic or suspected genetic diseases had been born. They found that there were tensions and conflicts within the family resulting from distorted concepts of genetic causation and from problems of reproductive and sexual adjustment. Ho (1971) found that the presence of a child with Down's syndrone in a family was a distinct burden to the child's brothers and sisters and a feeling of shame was aroused amongst them. Since many of the children affected with genetic diseases die in childhood there is pain and sorrow in the families following the death of the child. In Ho's study all the families reported that they regarded the death of the child in the same way as if a normal child had died and acted as such.

Not only does genetic disease impose a burden on society at present but this burden may increase. In addition to the possible genetic effect of ionising radiations and chemical mutagens, recently introduced medical and social practices such as improved treatment and selective abortion are potentially capable of leading to an increase in the incidence of genetic diseases and in the frequency of the corresponding deleterious alleles.

Although this potential for increase in the frequency of deleterious alleles is well known many authors seem to be relatively unconcerned. For example Medawar (1965) argues that the rate of genetic deterioration will be very slow and that during this time solutions will certainly

be found to cope with these difficulties. He states that 'present day skills are sufficient for present day ills'. However if the tools are available now they can be used now to alleviate suffering and cost to society both in the short term and in the long term. Crow (1973) argues this course since although there are many reasons not to rush headlong into a eugenics program, such as society's uncertainty about desirable ends and doubts about our ability to foresee all the consequences, much is already known about specific diseases and the results of selection are amongst the most predictable things in genetics.

(2) PRACTICES CONSIDERED

The practices whose effects will be considered in this thesis have been chosen because they are being adopted by an increasing number of individuals at present, or because concern has been expressed about their possible effects in the future. It is not claimed that these are the only practices which will operate now, or in the future, but they are some of the most important ones. They have been divided into two classes:-

(A) Dysgenic - resulting in an increase in frequency of deleterious alleles.

(B) Eugenic - resulting in a decrease in frequency of deleterious alleles.

In both (A) and (B) the change in disease incidence in any generation may not always be in the same direction as the change in gene frequency.

(A) Dysgenic practices

1. Improved treatment

With improved treatment affected individuals will have better survival rates and their reproductive fitness may be improved. This will result in more deleterious alleles being passed on to the next generation.

2. Selection of mate

It may be possible for individuals of a particular genotype to avoid having an affected child by selecting a marriage partner of a particular genotype. In AD (autosomal dominant) and XR (x-linked recessive) diseases all individuals with the deleterious allele will be at risk of having an affected child, regardless of their mate's

genotype.

In AR (autosomal recessive) diseases however, heterozygous carriers can avoid having affected offspring by selecting a mate who is homozygous normal. This would result in a decrease in disease incidence but an increase in gene frequency due to the birth of additional heterozygotes.

3. Selective abortion with reproductive compensation

If couples at risk of having an affected child were to practise selective abortion of affected fetuses or, in XR diseases, of male fetuses, there would be a reduction in disease incidence in the next generation. However if additional offspring were born to compensate for those aborted (reproductive compensation)* some of these would be unaffected carriers of the deleterious allele (except in AD diseases with complete penetrance). There would therefore be an increase in gene frequency.

The size of the changes would depend upon whether couples adopted the practice prospectively (before the birth of an affected child) or retrospectively (after the birth of an affected child). In the latter case the changes might be smaller because only a proportion of the offspring of couples at risk are born after the first affected child (see page 65).

(B) Eugenic Practices

4. Family limitation by carriers

If heterozygous carriers of deleterious alleles were detected before they reproduced they might decide to have a reduced number of offspring whether or not there was a high risk of any child being

* There is little practical evidence for reproductive compensation (see page 31).

affected. This would result in a decrease in both the disease incidence and the frequency of the deleterious allele in the next generation.

5. Family limitation by carriers at risk

Heterozygous carriers at risk of having an affected child might decide to limit their family size. This would apply to all carriers in AD and XR diseases but only to heterozygotes married to another heterozygote in AR diseases. As in (3) the changes in disease incidence and gene frequency would depend upon whether couples adopted the practice prospectively or retrospectively.

6. Family limitation by sibs of affected individuals

Normal sibs of affected individuals might have a reduced family size because of fear of having an affected child even though they might not actually be at risk. Some of these sibs would be carriers of the deleterious allele (except in AD diseases with complete penetrance) and there would therefore be a decrease both in disease incidence and gene frequency in the next generation.

7. Artificial insemination for spouses of carrier males

If carrier males were detected before they had any children their spouses might make use of AI (artificial insemination) by donor sperm. This would result in a decrease in both disease incidence and gene frequency in the next generation.

8. Artificial insemination for spouses of carrier males at risk

Spouses of carrier males at risk of having an affected child might make use of AI by donor sperm. This would apply to all carrier males in AD diseases but only to those married to a carrier female in AR diseases. It would not be applicable to XR diseases. Changes in disease incidence and gene frequency would depend upon whether adoption

of the practice was prospective or retrospective.

9. Selection abortion without reproductive compensation

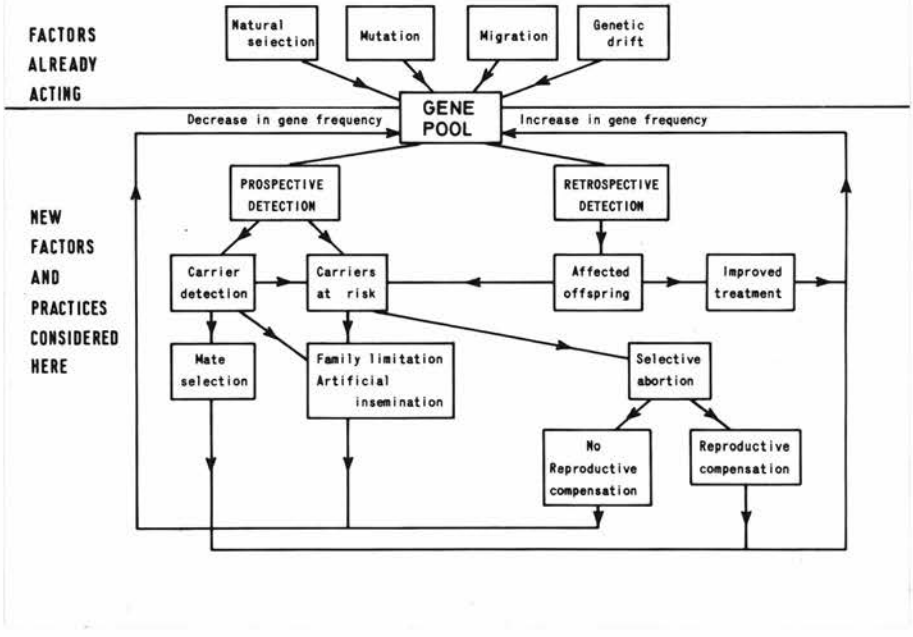
As stated earlier if couples at risk of having an affected child were to practise selective abortion of certain fetuses there would be a reduction in disease incidence in the next generation. If no additional offspring were born, family size would be reduced and there would be a decrease in gene frequency also.

Inter-relationships of practices and their effects on the gene pool

Figure 2.1 illustrates the inter-relationships of the various practices which could affect the frequency of a deleterious AR gene. For diseases of other modes of inheritance some of these practices would not be relevant e.g. selection of mate in AD diseases.

Note - For consistency the numbering system, used in this section for the various practices, will be used in all remaining sections of the thesis.

Figure 2.1 Diagram to illustrate the relationship between new practices affecting the frequency of a deleterious autosomal recessive gene.


FACTORS ALREADY ACTING
Natural selection
Mutation
Migration
Genetic drift
GENE POOL
Decrease in gene frequency
Increase in gene frequency
NEW FACTORS AND PRACTICES CONSIDERED HERE
PROSPECTIVE DETECTION
RETROSPECTIVE DETECTION
Carrier detection
Carriers at risk
Affected offspring
Improved treatment
Mate selection
Family limitation
Artificial insemination
Selective abortion
No Reproductive compensation
Reproductive compensation

(3) LITERATURE REVIEW

This thesis is concerned with the possible effects of various medical and social practices on the incidence of genetic diseases and the frequency of the corresponding deleterious alleles. Many authors have discussed certain aspects of this general topic in the past and the area of work is reviewed and discussed in this section. The studies can be broadly classified into two categories:-

Theoretical studies - dealing mainly with formulae and predictions for rates of increase in the frequencies and for new equilibrium frequencies of deleterious alleles.

Practical studies - dealing with the actual reproductive performance of families with genetic disease.

THEORETICAL STUDIES

Most of the theoretical work on this topic has considered the effect of a single practice acting in isolation and has mainly been concerned with possible dysgenic practices, such as improved treatment and selection of mates. Other workers have considered possible eugenic practices, such as family limitation by carriers and artificial insemination and practices which may be dysgenic or eugenic, such as selective abortion. In this section each of these practices will be discussed in turn.

(A) Dysgenic practices

1. Improved treatment

Carter (1972), Morton (1971) and others have examined the effects of improving the fitness of affected individuals for diseases of

different modes of inheritance.

(a) AD diseases

(i) Short-term changes

Carter (1972) for example, estimates that for a lethal AD disease an increase in the fitness of affected indivuduals to unity could increase the disease incidence to n times its initial value in generation n after the introduction of the treatment.

(ii) Long-term changes

Morton (1971) has derived formulae for the number of generations required to get half-way to a new equilibrium gene frequency when there is a change in the coefficient of selection against affected individuals. For example for an AD disease it can be calculated that if the coefficient of selection was originally 0.75 and this was ~~reduced~~ multiplied by a factor of 1/n it would take n generations for the gene frequency to go half-way to its new equilibrium value. The equilibrium gene frequency would be n times the initial frequency.

(b) AR diseases

(i) Short-term changes

In contrast to AD diseases there would only be a slow build up in incidence of AR diseases. Carter (1972) estimates that it would take of the order of 100 generations for the incidence of the disease to double for an increase in fitness from zero to one. Woolf and Goodwin (1967) have calculated that it would take of the order of 140 generations for the frequency of the gene for phenylketonuria to double (the disease incidence would then be four times the original incidence). This assumes that affected individuals originally had fitness of zero and the

gene was maintained solely by mutation.

(ii) Long-term changes

Using the same parameters as in (aii) above it can be calculated from the formulae of Morton (1971) that it would take $130\sqrt{n}$ generations to go half-way to the new equilibrium gene frequency. This would be about $3\sqrt{n}$ times the initial frequency if there was no heterozygote advantage. If there was heterozygote advantage the time required would be much shorter.

Turner (1968) has considered what effects improved fitness would have on the 'genetic load'. The 'genetic load' can be considered in this context as the percentage of the population eliminated by selection due to the locus. If the heterozygote has a large advantage over the normal homozygote the load at the new equilibrium will be slightly less than initially. If however, there is little heterozygote advantage the load may be several times greater at the new equilibrium. He estimates that there would initially be a decrease in the load and that it would take about 30 generations for it to reach its initial level.

(c) XR diseases

(i) Short-term changes

The time required for the doubling of incidence of an XR disease is intermediate between that for AD and AR diseases. Carter (1972) estimates it to be about five generations.

(ii) Long-term changes

Again using the same parameters as above and substituting in the formulae of Morton (1971) it would take $3n$ generations for the gene frequency to get halfway to the new equilibrium value. The new

equilibrium frequency would be about $\frac{\pi}{3\mu}$ times the initial frequency.

(d) MF diseases

For diseases which are partly genetic the calculations are more arbitrary and often empirical. For example, for pyloric stenosis which was previously fatal but can now be treated. Carter (1972) found that three percent of new patients were born of treated parents. This would give a three percent increase in the incidence per generation and the current incidence would be doubled in 25 generations. For other partly genetic diseases the rate of increase in incidence would depend on their initial incidence, the effectiveness of the treatment, the previous level of fitness and the incidence of the condition in children of affected parents.

2. Selection of mate

AR diseases

As explained in section (2) this practice will only be applicable to AR diseases.

(i) Short-term changes

Morton (1971) points out that the complete avoidance of marriages between heterozygotes, could reduce the frequency of deaths from sickle-cell anaemia in many African populations from some 100,000 per year to essentially zero. Fraser (1973) has studied the effect of complete avoidance of marriages between individuals heterozygous for deleterious AR alleles on the frequency of heterozygotes and the frequency of the deleterious allele. The effect would depend upon whether heterozygotes have a superior fitness. If so, the frequency of the recessive allele would increase until after many generations half the population would be heterozygous. He calculates that if

cystic fibrosis is at present maintained by a heterozygote advantage of 2.6 percent it would take 30 generations to double the heterozygote frequency whereas if only mutation pressure tended to increase the gene frequency it would take 2500 generations to double the frequency of heterozygotes.

(ii) Long-term changes

The effects of partial selection of mates on the frequencies of AR genes have been evaluated by Barker (1966) and Mayo (1970a). If affected individuals did not reproduce and a proportion (less than one) of heterozygotes were to seek a homozygous normal mate the incidence of affected individuals would slowly rise from a minimum in the first generation to the old level at equilibrium. The gene frequency would only be slightly increased in one generation even with heterozygote advantage and it would then rise slowly to a new higher equilibrium frequency.

Mayo (1970a) has also shown that there is little effect on gene frequencies at linked polymorphic loci in the short term and there is only an effect in the long term if there is tight linkage, or if there is no initial linkage and genotypic equilibrium.

(B) Eugenic practices

4. Family limitation by carriers and

5. Family limitation by carriers at risk

The possible effects of family limitation, either by all heterozygous carriers or by those at risk, have been studied by several workers.

(a) AD diseases

(i) Short-term changes

Complete family limitation by carriers of alleles which may give rise to AD diseases would reduce the incidence of such diseases to twice the mutation rate in one generation (Fraser (1973)). This minimum incidence is unlikely ever to be achieved in practice because complete ascertainment of individuals carrying the gene will rarely be possible. This is partly due to variation in penetrance of the gene and age of onset of the disease. The maximum proportionate reduction in incidence which can be achieved, is equal to the fitness of carriers of the allele.

(b) AR diseases

(i) Short-term changes

Prospective detection

Fraser (1973) has also discussed the effects of family limitation by heterozygous carriers in AR diseases. If all couples where both partners are heterozygous were to have no children the disease would be almost completely eliminated from the population in the next generation. If all carriers were to refrain from reproduction whatever the genotype of their marriage partner the deleterious allele would be eliminated in one generation. Fraser argues that since every individual carries several deleterious alleles in the heterozygous state, any generalised extension of the scheme to many loci would preclude reproduction altogether. However it might be applied to certain diseases serially or to a proportion of carriers in each generation.

Retrospective detection

For most diseases heterozygous couples are not detected until they have had an affected child. The reduction in incidence of the disease which would result if these couples subsequently had no children has been discussed by Fraser (1972b). He has tabulated the proportionate reduction in incidence for different means and variances of family size. This proportion is 0.23 for the family size distribution of the British 1961 Census. This is quite a substantial reduction which takes place in one generation. It would be much less if affected children were not diagnosed before subsequent children were born or if mean family size in the population was reduced. Fraser (1973) considers that the effect of this practice on the frequency of the deleterious allele would be negligable even in the long term. This is because few of the affected individuals whose birth is prevented would have reproduced anyway and the heterozygotes whose birth is prevented will only be a very small percentage of the total number.

(ii) Long-term changes

Barker (1966) has examined the change in equilibrium incidence of an AR disease and the corresponding change in gene frequency when there is partial exclusion of heterozygote marriages and a reduced family size in such marriages as do occur. When only the latter occurs there will be a decrease in both disease incidence and gene frequency. If there is a combination of both practices the disease incidence will always decrease but the gene frequency may either increase or decrease depending on the relative proportions of the two practices. Barker thus concludes that the optimum eugenic procedure would entail

minimisation of family size in heterozygote marriages.

Kidwell and Hagy (1971) studied the effects of complete family limitation in sibships with AR diseases, including sibs of affected individuals. This has only a small effect at equilibrium on both disease incidence and gene frequency.

(c) XR diseases

(i) Short-term changes

Retrospective detection

Fraser (1972b) has discussed the effect of family limitation by affected males and carrier females on the incidence of XR diseases. He discusses the case where heterozygous females have no more children after the birth of an affected child and shows that the proportionate reduction in disease incidence would be smaller than for AR diseases as a larger proportion of cases are due to new mutation. If the disease is lethal then the proportionate reduction in incidence in the next generation would be about 15 percent for the family size distribution of British 1961 Census. If there was a uniform family size of two the reduction in incidence would only be about nine percent.

(ii) Long-term changes

If the disease does not preclude reproduction in affected males the disease incidence would be reduced if these males were to have a reduced family size. Fraser (1973) has calculated that if affected males originally had a reproductive fitness of 0.2 there would be a 20 percent reduction in the incidence of the disease at equilibrium if these males did not reproduce. A further reduction would occur if there was family limitation by identified heterozygous females.

(d) MF diseases

(i) Short-term changes

Retrospective detection

In diseases with multifactorial inheritance the recurrence risk is usually low. It is not possible at present to identify high risk couples before the birth of an affected child. Smith (1970) estimates that the proportion of cases prevented by restricting family size after the birth of an affected child might be from 0.5 percent to a maximum of five percent. The actual proportion would depend on the incidence in the general population, the family size distribution and the recurrence risk in sibs of affected individuals.

7. Artificial insemination for spouses of carrier males and

8. Artificial insemination for spouses of carrier males at risk

Fraser (1973) has briefly discussed the possible effects of AI on the frequencies of deleterious alleles. AI would be equivalent to reducing the fitness of individuals with the deleterious gene and could have long term beneficial effects on the gene pool.

Dysgenic or Eugenic Practices

3. Selective abortion with reproductive compensation

9. Selective abortion without reproductive compensation

There are an increasing number of genetic diseases where it is possible to detect the fetal phenotype in utero and then offer an abortion if the fetus is found to be affected. Several workers have discussed the effects of such a practice on the incidence of genetic diseases and on gene frequencies.

The direction of the gene frequency change would depend upon whether or not there was reproductive compensation. If there was, additional unaffected carriers of the deleterious allele might be born. Haldane (1924) uses the term family selection to describe the situation where the number of survivors in each family is unchanged and offspring eliminated by natural selection are replaced by viable full sibs. This situation would occur in human populations if there was selective abortion with reproductive compensation. King (1965) has calculated that family selection would reduce the rate of selection by one third of that when there is no reproductive compensation for lethal recessive alleles and by one half for non-lethal recessive and dominant alleles.

(a) AD diseases

(i) Short-term changes

The effects of selective abortion in AD diseases have been discussed by Fraser (1973) and Motulsky et al (1971). The effects of selective abortion of affected fetuses on disease incidence and gene frequency would be virtually the same as for family limitation by carriers of the allele. Even if additional offspring were born to compensate for those fetuses aborted none of them would carry the deleterious allele. The reduction in incidence of the disease would be greatest for diseases where carriers of the deleterious allele have a high fitness.

Fraser (1973) has estimated the number of abortions of all fetuses with the deleterious allele, required, to reduce the frequency of an autosomal deleterious allele to the level imposed by mutation in one generation. If all couples continued reproduction until two unaffected offspring were born the number would be approximately $4qn$, where n is

the population size and q is the gene frequency. Since q is very small for dominant conditions Fraser regards this as a reasonable price to pay, especially since this would be a once and for all program, in that the gene frequency would remain very low for thousands of years. For Huntingtons chorea the cost would be about 2000 abortions per million population.

(b) AR diseases

(i) Short-term changes

Prospective detection

Motulsky et al (1971) have also considered the reduction in incidence of AR diseases as a result of selective abortion. If all couples at risk were detected prospectively then the disease could be temporarily eliminated in one generation. They consider a screening program based on premarital screening of females, followed by screening of male partners, intrauterine diagnosis and abortion, with reproductive compensation until two normal children are born. For several common AR diseases such a program would be economically feasible but for rarer diseases the number of tests required to prevent the birth of one affected child would become very large. The effects of this screening program on the frequency of the deleterious allele would be small in the short term, for the same reasons already discussed for family limitation by heterozygous couples (page 15); namely that affected individuals usually have low fitness and transmission of the deleterious allele is mainly through marriages involving one heterozygous parent.

Mayo (1970a) reached the same conclusion from calculations of gene

frequency changes if heterozygous couples practice selective abortion of all affected fetuses with reproductive compensation. Even with heterozygous advantage the gene frequency change would be very small. As in the case of AD diseases, with prospective detection of heterozygotes, it would require $4qn$ abortions to reduce the frequency of an AR deleterious allele to its mutational level in one generation. Motulsky *et al* (1971) do not consider that selective abortion provides a solution to the problem of eradicating genes causing AR diseases, because q is generally much higher and many of the fetuses who would have to be aborted would be heterozygotes and therefore not be affected.

Retrospective detection

Smaller changes in gene frequency and disease incidence would occur if couples were not ascertained until after the birth of an affected child. In the absence of reproductive compensation the changes in incidence discussed by Fraser (1972b) (page 15) would also apply when there was selective abortion rather than family limitation. Motulsky *et al* (1971) have estimated that if every mother with a previous child affected by an AR disease was to have selective abortion during subsequent pregnancies, until two clinically normal children were born, there could be a reduction of 12 percent to 34 percent in incidence of the condition in one generation. The actual reduction in incidence would depend upon how much reproductive compensation these couples previously practiced. The lower figure refers to the case where all couples previously had two children irrespective of their phenotype and the higher figure to the case where they all continued reproduction until two normal children were born. In practice the

percentage reduction would be intermediate between these extremes.

(ii) Long-term changes

Prospective detection

The long term effects of prospective detection of heterozygous couples and selective abortion with reproductive compensation are discussed by Fraser (1973) and Motulsky et al (1971). If the heterozygote originally had an advantage over the normal homozygote but as a result of improved environmental conditions this advantage is eliminated then the combined effect of selective abortion and loss of heterozygote advantage would be to cause a slight reduction in gene frequency. If however heterozygote advantage was maintained there would be a slight increase in the gene frequency because of the birth of additional heterozygotes. Fraser considers that the former possibility is more likely.

Retrospective detection

Hagy and Kidwell (1972) have studied the equilibrium frequencies of individuals of different genotypes if there is selective abortion of all affected fetuses conceived after the first affected child with complete reproductive compensation. They have shown that the equilibrium frequency of the deleterious allele would increase for fitnesses of heterozygotes ranging from a 5 percent advantage to a 5 percent disadvantage over the normal homozygote. However the increase would be very small except when there was heterozygous advantage and it would take many generations to reach the new equilibrium frequency.

(c) XR diseases

(i) Short-term changes

Retrospective detection

Possible changes in the incidence of XR diseases if heterozygous females were to practise selective abortion of certain fetuses have been considered by several workers. If heterozygous females were only ascertained after the birth of an affected child and all affected fetuses subsequently conceived were selectively aborted the decrease in the incidence in the next generation would be equal to that if these couples had no more children (Fraser (1972b)) i.e. about 15 percent.

(ii) Long-term changes

The long term effects of selective abortion in XR diseases have also been considered by Fraser (1972a) and the results are also discussed by Motulsky et al (1971). Fraser considers a uniform family size and three strategies of selective abortion, (A) prospective diagnosis of heterozygosity in the mother where reproduction ceases after the birth of a fixed number of normal children and (B) retrospective diagnosis of heterozygosity in the mother where reproduction ceases after the birth of a fixed number of children and (C) when it ceases after the birth of a fixed number of normal children. For each of these strategies he considers the effect of (1) abortion of all male fetuses, (2) abortion of affected male fetuses only and (3) abortion of affected male and carrier female fetuses.

Fraser considers firstly a uniform family size of two. In this case, if the disease is lethal, all but three of the nine possible combinations of strategy would result in a decrease in the equilibrium incidence of affected males to a minimum of one third of the initial value if heterozygous females are detected prospectively (A). If there was retrospective selective abortion of all males until two

children were born (B1), the equilibrium incidence of affected males would be unchanged but if there was retrospective selective abortion of all or affected males until two normal children were born (C1, C2) the incidence of affected males would actually increase but Fraser (1972a) calculates that there would be no substantial increase for at least 20 generations.

All strategies considered, apart from those where heterozygous females are aborted (3), would result in an increase in the frequency of these females at equilibrium to a maximum of 2.3 times the initial frequency when there is abortion of all male fetuses until two normal children are born (C1).

If family size is greater the same would be true, except that selective abortion of affected males until the desired number of normal children were born (C2) would result in a decrease, instead of an increase in the equilibrium incidence of affected males.

Although, as Fraser states, in most of the cases he considers there is a reduction in the incidence of affected males, the strategies which are now in use (i.e. retrospective selective abortion of all male fetuses (B1 and C1)), would result in no decrease in the equilibrium incidence of affected males and in case (C1) there would actually be an increase. The increase in the frequency of heterozygous females would be especially great in these two cases and thus there would be an increasing demand for selective abortion. However, these are only equilibrium values and short term changes in incidence would be of more practical importance.

(d) MF diseases

(i) Short-term changes

Retrospective detection

Selective abortion is rarely possible for multifactorial diseases such as the congenital abnormalities but it may be possible to detect affected fetuses in utero in the future (e.g. anencephaly, Brock and Sutcliffe (1972)). If couples who already had an affected child were to have subsequent pregnancies monitored and all affected fetuses were selectively aborted the incidence of these malformations could be reduced by the same amount as for family limitation by these couples i.e. up to about five percent.

PRACTICAL STUDIES

The studies described above are all purely theoretical and the frequency changes discussed would only occur if many individuals were to adopt the practices. Investigation of the actual reproductive performances of affected individuals and their relatives can give some insight into the changes which might occur in practice. This problem has been considered by several workers. They have mostly been concerned with the actual reproductive performances of affected individuals and of their parents. A few have considered other relatives of affected individuals.

1. Affected Individuals

Since most treatments have been introduced only recently few treated individuals have as yet reached reproductive age. Several studies have, however, been made of actual reproductive rates of individuals with those genetic diseases which do not preclude reproduction.

Cotter (1967) has discussed the reproductive performances of individuals in a large pedigree for the AD disease chondrodystrophy dating back to 1833. By comparing the early with the later generations he has estimated that the fitness* of chondrodystrophic dwarfs was initially close to unity but now they have a reduced fitness primarily because of withdrawal from the breeding population. Cotter suggests that this may be the result of social attitudes to the genetic disease

Reed and Neel (1959) made estimates of the fitnesses of individuals in families with Huntington's chorea from a survey of all cases in Michigan. They estimated the relative fitness of individuals heterozygous for the Huntington's chorea gene to be 0.8 compared to the general population and to be 1.01 compared to their homozygous normal sibs. This suggests that it is not the presence of the gene which reduces the fitness. The reduced fitness of both affected individuals and their normal sibs may result from a fear of developing the disease (in the latter) or of transmitting it to their children.

These two studies indicate that increasing the life span of affected individuals might not in itself result in their having more offspring if they still suffered much disability. However, the more normal the life affected individuals were able to live the more offspring they would be likely to have. For example if affected individuals no longer had to be institutionalised there might be an increase in the number of offspring they would have. Erlenmeyer-Kimling and Paradowski (1966) suggest that the decrease in length of hospitalisation may be one factor which has caused a change in the number of offspring of schizophrenics. By comparing two groups of patients admitted to

* The term 'Fitness' as used in this thesis includes both the effects of viability and Fertility.

New York hospitals in 1934-6 and 1954-6 they have shown that the reproductive rate is increasing and even surpassing that of the general population.

2. Parents of affected individuals

Many studies have been made of the reproductive rates of couples who have had an affected child. These indicate that several factors influence the parents' reproductive rate. These are the burden, the recurrence risk and parental understanding.

(i) Effect of burden

Hare et al (1966) followed up 120 families into which a child with a major central nervous system (CNS) malformation had been born. At interviews one month and six months after the birth of the child, about a half and a third, respectively of the mothers were reluctant to have more children. Ho (1971) followed up families with a child with Down's syndrome 2-4 years after the birth of the child. Parents whose affected child was dead more often had further children than those whose child was alive. Boon (1972) found that the birth of a child with Fallot's tetralogy was not a great deterrent against having further children. There was however a tendency for the parents to postpone having further children until the condition of the affected child had improved and a greater willingness to accept sterilisation after three or four children.

These results suggest that if the disease produces severe disability and there is little or no therapy available (e.g. Down's syndrome or CNS malformations), parents are reluctant to have further children unless the affected child dies early. The parents in Ho's study felt that they had to devote themselves to the care of the affected child and actual fear of having another affected child was

dominant in only a few cases. On the other hand if affected individuals are less severely disabled, or effective therapy is available, as for Fallot's tetralogy they are more likely to have further children.

(ii) Effect of recurrence risk

Of the families with CNS malformations (Hare et al 1966) only 40 percent had been told of the risk of recurrence. The authors of the other studies do not give the exact proportions of parents, who had been told about the risks.

There is evidence that if parents are advised of the risk of future children being affected, this also influences their tendency to have more children. Carter et al (1971) report the results of a follow-up of 455 couples seen at a genetic clinic who wished for advice on the risks of recurrence of serious disorders in their children. They tried as far as possible to distinguish couples deterred by the risk, from those who did not want further children for other reasons. They found that when the recurrence risk was high (greater than 10 percent) two-thirds of the couples were deterred by the risk from planning further children but when the risks were low (less than 10 percent) only about a quarter were deterred by the risk. A closer study of the high risk group showed that the decision to take the risk usually depended on whether a further affected child would have a serious long term handicap. They found that the majority of instances where the parents were not deterred involved conditions where any further child if affected was likely to die young, where a treatment was available, or where the condition was relatively mild.

Similar results were obtained by Emery et al (1973) in a follow up study of 104 families referred for genetic counselling. Of those

at high risk 82 percent were deterred from having further pregnancies and of those at low risk 23 percent were deterred. In four of the ten high risk couples not deterred this was because they had no living children and the disease usually resulted in death in early infancy. Of the ten low risk couples deterred three had completed their family, two were divorced and one had a severely handicapped child.

Emery et al (1972) also carried out a follow-up study of women with one or more relatives with Duchenne muscular dystrophy. They found that 88 percent of women at high risk of having an affected son or carrier daughter did not want any more children and of those at low risk 50 percent did not want further children. Although it is not known how many of the couples had already completed their family the large proportion not wanting further children particularly in the low risk group is probably because Duchenne muscular dystrophy is a severely disabilitating disease with no therapy available at present.

Leonard et al (1972) studied the attitudes to further reproduction of parents of children affected with cystic fibrosis, phenylketonuria, Down's syndrome and a non genetic disease rheumatoid arthritis. They found that 20 percent of parents of children with the latter two diseases were against having further children even though the risks of further children being affected were very low. This was presumably because of the burden of bringing up a severely handicapped child. 70 percent of parents of children with cystic fibrosis were against having further children. Here in addition to the burden there is a 25 percent risk that a future child would be affected. In the case of parents of children with phenylketonuria where the risk is the same as above but

effective therapy is available only 14 percent were against having further children.

(iii) Effect of parental understanding

Any influence on the parents' reproductive rate of a risk of a future child being affected would depend on the parents' understanding of the genetic implications of the disease. Carter et al (1971) and Emery et al (1972, 1973) found that in general couples had understood the risks they had been given. However Leonard et al (1972) found that 19 out of 61 families completely failed to understand the information provided and eight understood it only imperfectly. This may be due to the fact that the families studied by Carter were derived from a higher socio-economic level and had all asked for counselling, whereas the families studied by Leonard were from lower socio-economic classes and were less well educated and were sometimes hostile at interview. In Leonard's study however he found no significant relationship between genetic knowledge and reproductive outcome. Having more children seemed more related to maternal age and religion and this may be largely due to the fact that 28 of the 76 families were Roman Catholic.

(iv) Extent of adoption of new practices

Carter (1971), Emery et al (1972, 1973) and Leonard et al (1972) also discussed the practices adopted by the couples subsequent to counselling. The families studied by Carter (1971) were all seen initially between 1952-64 and were followed up three to ten years later. All the couples who were undeterred went on to have children some of whom were affected and some normal. Of 169 couples who were deterred six were divorced and three separated and two made use of artificial insemination by donor but this was not discussed unless the

couple asked for it. 35 of these couples had unplanned pregnancies eight having a termination, another six being refused a termination.

Emery et al (1973) followed up couples seen between 1965-69. 56 couples did not want further children but five had unwanted pregnancies all undergoing therapeutic abortions. One of the women who was undeterred had an abortion of a male fetus. The families discussed by Emery et al (1972) with Duchenne muscular dystrophy were also seen from 1965-69. Of the 41 couples who did not want further children only two had unwanted pregnancies and these were aborted. Of the nine couples undeterred two had amniocentesis, one fetus subsequently being aborted when it was found to be male.

The couples studied by Leonard et al (1972) were seen between 1969-70. Those with children with cystic fibrosis (CF), phenylketonuria (PKU) and Down's syndrome (DS) were asked their attitudes to sterilisation, to abortion of any pregnancy and to amniocentesis and selective abortion if this were to become available. 51 percent CF, 30 percent DS and 14 percent PKU couples were in favour of sterilisation. Only 18 percent CF, 13 percent DS and 14 percent PKU couples were in favour of abortion of any pregnancy but unfavourable attitudes to abortion became favourable in the context of antenatal diagnosis, 36 percent CF, 53 percent DS and 29 percent PKU being in favour of selective abortion. This was despite the fact that 38 percent of the couples were Roman Catholic.

Although the numbers of patients involved is small these figures do suggest some possible trends. For example there may be an increase in the tendency to divorce if couples know there is a risk of their having an affected child. Carter states that in view of the age of

the couples one percent of them would be expected to be divorced and therefore five out of 455 currently divorced is not excessive. However at least four out of 169 deterred couples is nearly two and a half times what would be expected.

A greater proportion of couples in Carter's study had unplanned pregnancies than in Emery's which could indicate an increase in use of effective contraceptive measures by the couples but it might just reflect the longer time period over which the couples were followed up.

Only half the couples in Carter's study wanted an unplanned pregnancy to be terminated. The difficulty experienced by some of Carter's patients in getting a pregnancy terminated on the grounds of a genetic risk to the fetus, no longer applies, since the passing of the 1967 Abortion Act in the U.K. All the couples discussed by Emery et al (1972, 1973) who had unplanned pregnancies wanted them terminated, indicating an increased acceptance of abortion. The increased acceptance of abortion when a fetus can be positively identified as being affected or normal can be clearly seen from the study of Leonard et al (1972). It would have been interesting to see what proportion of couples preferred selective abortion to family limitation and what proportion preferred family limitation.

(v) Reproductive compensation

It has been suggested that couples having abortions or whose children died in infancy might have additional pregnancies so that their mean family size would be no different from that of other couples. If this did in fact occur it would indicate that couples practising selective abortion would not have a reduced number of living offspring but additional unaffected children would be born to compensate

for those aborted.

Newcombe (1965) studied the reproductive performances of mothers following stillbirths, infant death from erythroblastosis, hemorrhagic disease and asphyxia and following the birth of a child with Down's syndrome who did not die. When these mothers were compared with another group with similar ages and parities there was no evidence for reproductive compensation except for asphyxia and Down's syndrome. In the former case it was thought to be due to an association of asphyxia and high fertility in a sub-population in the study.

Reed (1971) has reviewed several studies for evidence of reproductive compensation with particular reference to Rhesus hemolytic disease. He found little support for the idea that it is a general phenomenon. However, although the results presented in the papers he reviews do not give strong evidence in favour of reproductive compensation, they do suggest a small effect.

Only two of the studies reviewed by Reed (1971) were concerned with women who had had an abortion, rather than a stillbirth or a child who had died in infancy. In one of these, James (1963) found a significantly greater number of pregnancies in women prone to abortion than in other women. Reed (1971) suggests that this may have been due to the existence of a class of women having increased tendency towards abortions and an increased number of pregnancies. However it could indicate that if there was selective abortion of certain fetuses, reproductive compensation would occur.

3. <u>Other Relatives of Affected Individuals</u>

In addition to the parents of the affected individual the reproductive rates of other relatives may be affected by the presence of an affected

individual in the family.

Tips and Lynch (1963) found a reduction in pregnancy rate both in the parents and in paternal and maternal aunts after the birth of an affected child. It is not possible from their results to calculate the reduction in reproductive rate of aunts only, as the results for aunts and parents were combined in their paper.

Reed and Neel (1959) compared the fertility of sibs of individuals with Huntington's chorea with individuals in the general population and they found the relative fertility of non-choreic sibs to be about 0.77. Most of these individuals had an affected parent and it is likely to be the presence of an affected parent, rather than an affected sib, which affects their reproductive rate. This is because many of the individuals affected at the time of the study would not have been affected at the time they and their sibs reproduced.

These two studies therefore indicate that the presence in a family of an affected individual influences the reproductive rate of a number of different relatives. However Cotter (1967) could find no evidence for a difference in fitness between sibs of individuals with chondrodystrophy and the general population in the pedigree he investigated.

Erlenmeyer-Kimling and Paradowski (1966) found no difference in fitness amongst the sibs of schizophrenics compared with the general population in 1934-1936 but in 1954-56 their fitness was 1.4 times that of the general population indicating a newly emerging sibling advantage. It seems therefore that there may be an effect on reproductive fitness in relatives in some diseases but not in all.

CONCLUSIONS

The theoretical studies indicate that there would be changes in the incidence of genetic diseases and in the frequencies of deleterious alleles, as a result of the introduction of practices such as improved treatments, selection of mates, family limitation, artificial insemination and selective abortion. At present few couples obtain genetic advice and ~~those who do so~~ clinicians may be unwilling to advise couples to adopt new techniques, such as selective abortion, until their safety and reliability can be proved. With the improvement of these techniques, extension of genetic counselling services and improvement in methods of detection of individuals at risk, the gene frequency changes may become larger. The results of the follow-up studies indicate that most couples at high risk of having an affected child are deterred from having further children, although there was an indication that as treatments become available fewer couples would be deterred from having further children.

These results are all integrated with those of the thesis later and discussed in a general discussion section.

(4) THE DISEASES AND THEIR FREQUENCY CHANGES TO BE DISCUSSED

In this section the modes of inheritance and the categories of age of onset of the diseases to be considered, will first be described. The current forces affecting the incidences of these diseases and the frequencies of the corresponding alleles will then be discussed. Lastly there will be a description of the scope of the present study and the assumptions and conventions used throughout.

(A) Diseases Considered

(i) Modes of Inheritance

Genetic diseases of four main modes of inheritance have been considered.

1. Autosomal recessive (AR) e.g. cystic fibrosis
2. Autosomal dominant (AD)
   (a) with complete penetrance e.g. achondoplasia
   (b) with incomplete penetrance e.g. osteogenesis imperfecta
3. X-linked recessive (XR) e.g. haemophilia
4. Multifactorial (MF) e.g. spina bifida. (These are diseases whose manifestation may depend upon the joint effects of many genes and of the environment).

(ii) Age of Onset

Three different categories of age of onset have been discussed. Individuals are only considered to be at a selective disadvantage after onset of the disease.

(a) Onset is at birth or before the birth of any subsequent children to the parents of the affected individual.

(b) Onset takes place after the parents of the affected individual

have completed their family but before the individual himself starts his family.

(c) Onset is after the affected individual has completed his family.

(B) Current State

At any particular time the frequency of a gene in the population is the result of a balance between forces tending to increase its frequency and other forces tending to decrease its frequency. In a large random mating population, in the absence of intervention by man, most deleterious alleles are maintained at low frequencies. This is because of strong negative forces tending to decrease their frequency and relatively weak positive forces tending to increase their frequency. If these existing forces remain constant for a long time, an equilibrium situation will arise in which the gene frequency will remain constant from generation to generation. If the forces do not remain constant there will be a resulting trend in gene frequency either upwards or downwards. Recently introduced practices such as those discussed in sections (2) and (3) introduce new forces which may change the frequency of deleterious alleles.

In practice the existing forces affecting frequencies of deleterious alleles will have several components e.g. mutation and natural selection. The sizes of these forces and the resulting current trends in gene frequency are very difficult to measure especially in human populations. In this thesis no attempt has been made to measure possible changes in frequency due to these existing forces. Interest is centred on new forces and their possible effects on disease incidence and gene frequency.

All the changes calculated are those which would result from the new forces over and above any change due to natural selection against affected individuals. This makes it possible to measure the relative effects of the new forces. If there is initial equilibrium the effect of natural selection will be balanced by the effect of other forces such as mutation and so the overall change in frequency would be equal to that due to the new force. In the absence of initial equilibrium the change due to the new force must be added on to those due to natural selection and to mutation etc. to obtain the overall change.

(C) Scope of the Study

The workers whose studies are described in the literature review have mainly been concerned in estimating new equilibrium values of the gene frequency which will only be attained after several or many generations. Long term gene frequency changes resulting in new equilibrium values would be less important than short term ones. The reaching of a new equilibrium value would depend on medical practices remaining constant over many generations. This is unlikely with rapid developments in the fields of treatment and detection of individuals at risk.

They have also been mainly concerned with the effects of single practices acting in isolation. Although these effects are of theoretical interest, it is far more probable that several practices would operate simultaneously and the resulting changes in gene frequency would depend upon the effects of several practices.

For these reasons, in this thesis, effort has been concentrated on estimating single generation changes in disease incidence and gene

frequency both by practices operating alone and in combination.
The study is aimed at estimating:

1) The relative importance of different practices in causing changes in disease incidence and gene frequency.
2) The relative importance of the practices which are potentially dysgenic and those which are potentially eugenic.

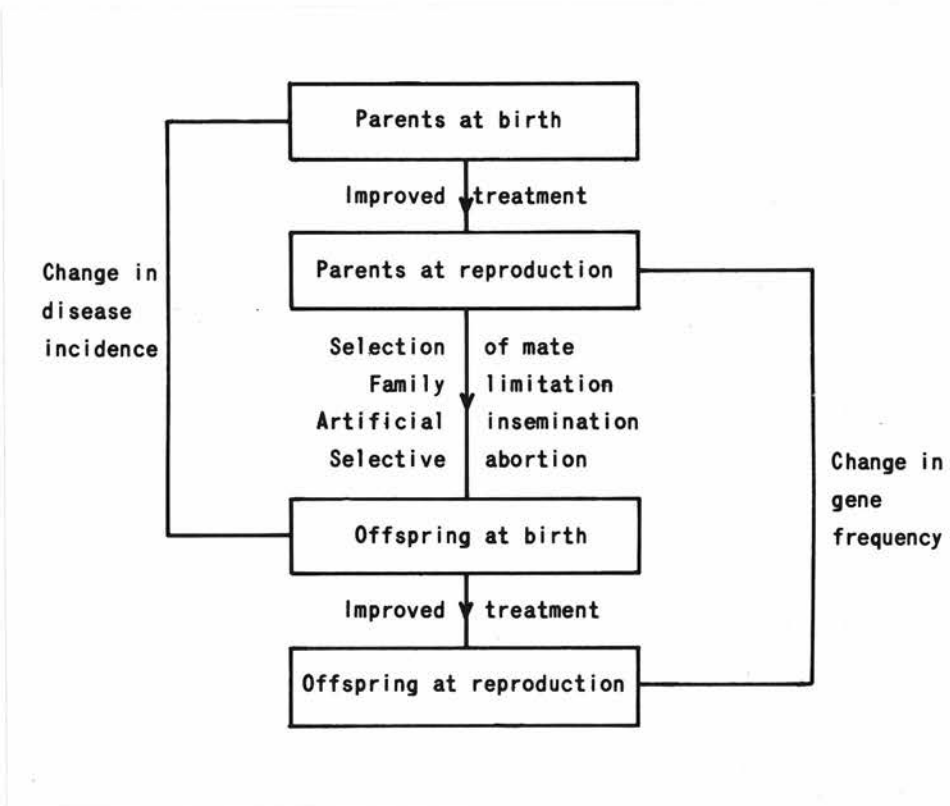
(D) Assumptions and Conventions

For all classes of disease considered, unifactorial and multifactorial, the change in disease incidence is taken to be the difference between that in the offspring generation at birth and that in the parental generation at birth. The change (Δ_1) which results from natural selection alone is subtracted from the change (Δ_2) which results from a particular practice together with natural selection to obtain the net change ($\Delta_2 - \Delta_1$) due to the practice.

It is possible to ~~measure~~ calculate actual gene frequency changes only for unifactorial (AR*, AD, XR) diseases, as in the case of MF diseases individual genes and their frequencies are not known. The gene frequency in the offspring generation at birth does not necessarily reflect changes in the genotype distribution among the offspring. If mating is non-random as in mate selection, or if selective abortion with reproductive compensation is practised, the genotype frequencies of offspring may be changed but the gene frequencies may not. Then if fewer affected individuals and more unaffected carriers were born the offspring would pass on more deleterious genes to the next generation when there would be an increase in gene frequency. In order to consider the change as if it were in the current generation (as for the rest of the practices), the gene frequency change is

* For any particular AR disease, the value of q (the initial gene frequency) can only be calculated by assuming that the population is in Hardy-Weinberg equilibrium.

Figure 4.1 Diagram to show how the changes in disease incidence and gene frequency are measured and where the practices studied act.


Parents at birth
Improved treatment
Parents at reproduction
Change in disease incidence
Selection of mate
Family limitation
Artificial insemination
Selective abortion
Change in gene frequency
Offspring at birth
Improved treatment
Offspring at reproduction

measured throughout as the difference between the frequency in the parents at reproduction and the frequency in their offspring at reproduction. The change due to existing forces, is subtracted as before.

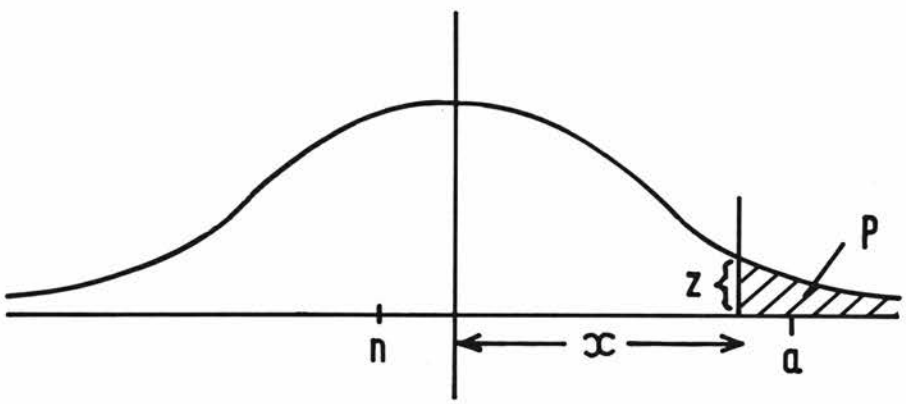
A diagramatic representation of how the changes in disease incidence and gene frequency have been measured and where the practices studied act is shown in Figure 4.1.

For unifactorial diseases it is assumed that the parents have Hardy-Weinberg genotype frequencies at birth. Affected homozygotes in AD diseases and affected females in XR diseases are ignored as their frequencies are very small. If affected individuals have low fitness,*

For multifactorial diseases a different net of conventions and assumptions is used. It is assumed that there is an underlying continuous and normally distributed liability to the disease with zero mean and unit variance as shown in Figure 4.2. The proportion of individuals exceeding the threshold of liability is affected, this proportion being denoted by P. The mean liability of any group of individuals is expressed as the number of standard deviations from the mean of the parental generation. From the heritability of liability (h^2) to the disease and the liability of individuals who reproduce it is possible to calculate the mean liability and hence the disease incidence in the offspring (Falconer (1965)).

* With improved treatments, family limitation and selective abortion without reproductive compensation there will be a change in the total number of offspring born when the practice is adopted. For simplification of the Formulae this has been ignored in most of the calculations and its effect on the changes can be shown to be very small.

Figure 4.2 Diagram to illustrate the conventions and assumptions used for multifactorial diseases. For definition of parameters see Table 5.1.


P
z
n
x
a

(5) DERIVATION OF CHANGES IN DISEASE INCIDENCE AND GENE FREQUENCY

Changes in disease incidence and gene frequency have been calculated for diseases of four modes of inheritance at different onset ages and for all the practices, described in section (2), which are applicable for a particular mode of inheritance. As the methods of calculation of the changes are very similar throughout, only a few examples are given in detail in this section. The variables and symbols used are summarised in Table 5.1 and the complete set of results is tabulated in Tables 5.2 - 5.11.

As was discussed in section (4D) it is necessary to estimate the effect of natural selection alone, in order to obtain the net effect of a particular practice. Therefore in section (5A) the effect of natural selection is calculated for diseases of each mode of inheritance. In section (5B) the net effects of three of the new practices are calculated. Firstly the joint effect of the new practice and natural selection is obtained. The effect of natural selection alone is then subtracted from this to obtain the net effect of the practice.

(A) Effect of natural selection

For simplicity it is assumed that there is a constant natural selection force against affected individuals. Possible effects of positive selection forces resulting from factors such as heterozygote advantage have not been considered in this section.

Heterozygote advantage may be an important factor in the incidence of some diseases in certain populations e.g. sickle-cell anaemia in African populations (Allison, 1964). It has also been suggested that heterozygote advantage occurs in Tay-Sachs disease in Jews

TABLE 5.1

Variables and symbols used

Variable	Symbol
All modes of inheritance	
Proportion of individuals who adopt a practice	c_i
Proportion of couples who adopt a practice	c_m
Proportionate change in fertility of couples	f'_m
Unifactorial diseases	
Dominant allele	A
Recessive allele	a
Proportionate change in fertility of individuals of genotype *i*	f'_i
Frequency of normal allele	p
Frequency of deleterious allele	q
Proportion of the offspring of couples at risk who are born after the first affected child	p_r
Proportion of the offspring of couples at risk who are normal sibs of affected individuals	p_s
Coefficient of selection against individuals of genotype *i*	s_i
Change in s_i	s'_i
Proportion of individuals of genotype *i* ascertained	w_i
Penetrance of *A* gene in *Aa* individuals	y
Multifactorial diseases	
Mean liability of affected individuals	a
Mean liability of individuals (couples) exceeding a given liability x' (x'')	a_x
Proportion of individuals who adopt a practice	c_x
Proportionate change in fertility	f'_x
Heritability of liability to the disease	h^2
Mean liability of normal individuals	n
Mean liability of individuals (couples) not exceeding a given liability x' (x'')	n_x

TABLE 5.1 (contd.)

Variable	Symbol
Multifactorial diseases	
Proportion of all affected individuals who are born after the first affected child in the family	p_{rm}
Proportion of individuals who are normal sibs of affected individuals	p_{sm}
Disease incidence in the parental generation	P
Proportion of individuals (couples) exceeding a given liability x' (x'')	p_x
Relative loss of fitness of affected individuals	s_f
Change in s_f	s'_f
Proportion of individuals ascertained	w_x
The abscissa at the threshold	x
The ordinate at x	z

(Myrianthopoulos and Aronson, 1966) and in cystic fibrosis in Caucasians (Danks et al, 1965). Mayo (1970b), however, finds the evidence for greater fertility of heterozygotes in cystic fibrosis and Tay-Sachs disease inadequate.

Formulae for changes in incidence and in gene frequency for diseases where there is heterozygote advantage can be calculated in a similar manner to those for diseases where there is no heterozygote advantage. The formulae are given in appendix (3). They are more complex as the changes are dependent both upon the initial gene frequency and on the coefficients of selection against normal and affected homozygotes. Using figures from Falconer (1960) possible changes for sickle cell anaemia in African populations have been calculated and these are plotted in Figures A3.1 and A3.2. Differences between these results and those for diseases where there is no heterozygote advantage are discussed in section (6).

1) AR diseases

Consider an AR disease with individuals of genotype aa affected. In the parental generation at birth the genotypes have the following frequencies and fitnesses:-

Genotype	AA	Aa	aa
Frequency	p^2	2pq	q^2
Fitness	1	1	$1-s_{aa}$

If selection operates between birth and reproduction of the parental generation the couples at risk of having affected offspring have frequencies and fitnesses as follows:-

Mating type	Frequency	Fitness	Proportions of offspring		
			AA	Aa	aa
Aa x Aa	$4p^2q^2$	1	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
Aa x aa	$4pq^3$	$(1-s_{aa})$	0	$\frac{1}{2}$	$\frac{1}{2}$
aa x aa	q^4	$(1-s_{aa})^2$	0	0	1

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{1}{4}.\ 4p^2q^2 + \frac{1}{2}.\ 4pq^3\ (1-s_{aa}) + q^4\ (1-s_{aa})^2$

$$\doteq q^2\ (1-2qs_{aa})$$

The change in disease incidence between parental and offspring generations due to natural selection is therefore approximately $q^2\ (1-2qs_{aa}) - q^2 = -2q^3 s_{aa}$

(ii) Gene frequency The gene frequency change is measured between the parental generation at reproduction and the offspring generation at reproduction. The approximate frequency of a in the parental generation at reproduction is $\frac{1}{2}\ (2pq) + q^2\ (1-s_{aa}) \doteq q - s_{aa}q^2$ As a result of selection against affected individuals the frequency of a is reduced by approximately $s_{aa}q^2\ (1-2qs_{aa})$ by the time the offspring reproduce. Therefore the approximate change in gene frequency due to natural selection is $-s_{aa}q^2$

2a) AD diseases with complete penetrance

Consider an AD disease with individuals of genotype Aa affected. In the parental generation at birth the genotypes have the following frequencies and fitnesses:-

Genotype	Aa	aa
Frequency	2pq	p^2
Fitness	$1-s_{A-}$	1

(i) Disease incidence Following the same method as above couples at risk of having affected offspring have frequency and fitness as follows:-

Mating type	Frequency	Fitness	Proportions of offspring	
			Aa	aa
Aa x aa	$4p^3q$	$(1-s_{A-})$	$\frac{1}{2}$	$\frac{1}{2}$

The approximate incidence of affected individuals in the offspring is $\frac{1}{2}.\ 4p^3q\ (1-s_{A-}) = 2p^3q\ (1-s_{A-})$

Taking $p \doteq 1$ the change in disease incidence due to natural selection is approximately $2q(1-s_{A-})-2q = -2qs_{A-}$.

(ii) Gene frequency The approximate frequency of A in the parental generation at reproduction is $\frac{1}{2}.\ 2pq\ (1-s_{A-}) = q(1-s_{A-})$

As a result of selection against affected individuals one half of whose genes are A the frequency of A is reduced by approximately s_{A-} $s_{A-}.\frac{1}{2}.\ 2p^3q\ (1-s_{A-})$ by the time the offspring reproduce. Therefore the approximate change in gene frequency due to natural selection is $-s_{A-}\ q(1-s_{A-})$

2b) AD diseases with incomplete penetrance

For AD diseases with incomplete penetrance the calculations are exactly the same as for (2a) except that only a proportion y of individuals of genotype Aa are affected and at a selective disadvantage.

Therefore the overall fitness of Aa individuals is $(1-ys_{A-})$.

(i) Disease incidence Following the same method as above the approximate incidence of affected individuals in the offspring is $4p^3q\ (1-ys_{A-}).\frac{y}{2}$ (since half the offspring of heterozygotes are heterozygous and a proportion y are affected). The approximate change in disease incidence due to natural selection is therefore

$$2qy\ (1-ys_{A-}) - 2pqy \doteq -2qy^2s_{A-}$$

(ii) Gene frequency The approximate frequency of A in the parental generation at reproduction is $\frac{1}{2}.\ 2pq\ (1-ys_{A-}) = q(1-ys_{A-})$. As a result of selection against affected individuals the frequency of A is reduced by approximately $\frac{1}{2}\ s_{A-}.2qy\ (1-ys_{A-})$ by the time the offspring reproduce. Therefore the approximate change in gene frequency due to natural selection is $-qys_{A-}\ (1-ys_{A-})$

3) XR diseases

Consider an XR disease with males of genotype aY affected. In the parental generation at birth/the genotypes have the following frequencies and fitnesses:-

	Females		Males	
Genotype	AA	Aa	AY	aY
Frequency	p^2	2pq	p	q
Fitness	1	1	1	$1-s_a$

Couples at risk of having affected offspring have frequencies and fitnesses as follows:-

Mating type	Frequency	Fitness	Proportions of offspring			
			Females		Males	
			AA	Aa	AY	aY
Aa x AY	$2p^2q$	1	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
Aa x aY	$2pq^2$	$1-s_a$	0	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate disease incidence amongst male offspring is $\frac{1}{2}.\ 2p^2q + \frac{1}{2}.\ 2pq^2\ (1-s_a) \doteq q(1-qs_a)$
The change in incidence due to natural selection is therefore approximately $q - q^2s_a - q = -q^2s_a$

(ii) Gene frequency Two thirds of the genes at an X-linked locus are carried by females and one third by males. Since half the genes of heterozygous females and all the genes of affected males are a the approximate frequency of a in the parental generation is $\frac{2}{3}\ [\frac{1}{2}.\ 2pq] + \frac{1}{3}\ [q(1-s_a)] \doteq q(1-\frac{1}{3}s_a)$. As a result of selection against affected males who contribute one third of all the genes at the locus the frequency of a is reduced by approximately $\frac{1}{3}\ s_a q\ (1-qs_a)$ by the time the offspring reproduce. Therefore the approximate change in gene frequency due to natural selection is $-\frac{1}{3}\ qs_a$.

4) MF diseases

Consider an MF disease with individuals having a normal distribution of liability to the disease as in Figure 4.2. In the parental generation at birth, normal and affected individuals have the following frequencies and fitnesses.

Phenotypes	Normal	Affected
Frequency	1-P	P
Mean liability	n	a
Fitness	1	$1-s_f$

The mean liability of the offspring is the product of the heritability and the mean liability of their parents. If selection operates between the birth and reproduction of the parental generation the mean liability of the offspring is $h^2 [n(1-P) + aP(1-s_f)]$. Substituting $n = \frac{-z}{1-P}$ and $a = \frac{z}{P}$ the mean liability becomes $-zh^2 s_f$. Since the parental generation is taken to have a mean liability of zero at birth this expression is the difference between parental and offspring generations in mean liability at birth. The difference in disease incidence is approximately z times the difference in mean liability, since z is the height of the curve at the threshold point. Thus the approximate change in disease incidence is $-z^2 h^2 s_f = a^2 P^2 h^2 s_f$.

(B) Effects of practices

The effects of three of the new practices are calculated in this section for diseases of each mode of inheritance. These examples illustrate the methods used for all the practices considered. The first example deals with the effects of improved treatment as this is the simplest method. The second example deals with the measurement of the effects of prospective family limitation by carriers illustrating the method of calculation when there is a change in the fitness of individuals other than those who are affected. In the third example the most complex method of calculation, that for prospective selective abortion with reproductive compensation is described. This gives the

method used when the fitness of couples rather than that of individuals is considered. Here there is also a change in the genotype distribution of the offspring. For each of these practices the changes in disease incidence and gene frequency for early onset AR, AD (complete penetrance) and XR diseases and changes in disease incidence for early onset MF diseases are calculated. Changes resulting from other practices and for AD diseases of incomplete penetrance are calculated in Appendix 1.

1) AR diseases

Improved treatment (1)

Suppose an improved treatment for the disease has the effect of reducing selection against aa individuals by an amount s'_{aa}. The disease incidence and gene frequency changes are calculated by the same method as in section (A) replacing s_{aa} by $(s_{aa} - s'_{aa})$.

(i) Disease incidence The change in disease incidence between parental and offspring generations is approximately $-2q^3(s_{aa} - s'_{aa})$. Subtracting the effect of natural selection alone, the net change due to the practice is approximately $2q^3 s'_{aa}$

(ii) Gene frequency Similarly the difference in gene frequency between the parental and offspring generations is approximately $-(s_{aa} - s'_{aa})q^2$. Subtracting the effect of natural selection alone the net change due to the practice is approximately $s'_{aa}q^2$

Family limitation by carriers (4)

- prospective

Suppose a proportion w_{Aa} of heterozygous carriers is ascertained before they have had any children (i.e. prospectively) and of these a proportion c_i subsequently reduce their intended family size by a proportion f'_{Aa}. Putting these terms together the fitness of carriers is $(1 - w_{Aa}c_i f'_{Aa})$. Assuming that fitnesses are multiplicative the fitness of heterozygous (Aa x Aa) couples is $(1 - w_{Aa}c_i f'_{Aa})^2$.

(i) Disease incidence Since most affected individuals are the offspring of couples where both partners are heterozygous the approximate reduction in disease incidence is calculated by only considering couples of this type. These couples have frequency and fitness as follows:-

Mating type	Frequency	Fitness	Proportions of offspring		
			AA	Aa	aa
Aa x Aa	$4p^2q^2$	$(1-w_{Aa}c_i f'_{Aa})^2$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$

The difference in disease incidence between the offspring and parental generations is then approximately $\frac{1}{4}.\ 4p^2q^2\ (1-w_{Aa}c_i f'_{Aa})^2 - q^2$

$$= -q^2 w_{Aa}c_i f'_{Aa}\ (2-w_{Aa}c_i f'_{Aa})$$

Subtracting the effect of natural selection alone the approximate net change due to the practice is $-q^2 w_{Aa}c_i f'_{Aa}\ (2-w_{Aa}c_i f'_{Aa})$

(ii) Gene frequency The approximate frequency of a in the parental generation is $q-s_{aa}q^2$. Since half the genes of heterozygotes are a the reduction in gene frequency due to family limitation is approximately $\frac{1}{2}\ (2pq\ w_{Aa}c_i f'_{Aa}) \doteq q\ w_{Aa}c_i f'_{Aa}$

The reduction in gene frequency due to selection against affected individuals born is approximately $s_{aa}q^2 (1-w_{Aa}c_i f'_{Aa})^2$. Therefore subtracting the effect of natural selection alone the net change in gene frequency due to the practice is approximately

$$-q\, w_{Aa}c_i f'_{Aa} - s_{aa}q^2 (1-w_{Aa}c_i f'_{Aa})^2 + s_{aa}q^2 \doteq -q\, w_{Aa}c_i f'_{Aa}$$

Selective abortion with reproductive compensation (3)

- prospective

Suppose a proportion w_m of couples where both partners are heterozygous is ascertained prospectively and a proportion c_m of these practise selective abortion of affected fetuses with reproductive compensation. Heterozygous couples (Aa x Aa) have frequencies as follows:-

	Frequency	Proportions of offspring		
		AA	Aa	aa
Practising selective abortion	$4p^2q^2w_m c_m$	$\frac{1}{3}$	$\frac{2}{3}$	0
Not practising selective abortion	$4p^2q^2(1-w_m c_m)$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{1}{4}.\ 4p^2q^2 (1-w_m c_m) \doteq q^2 (1-w_m c_m)$

Following the same reasoning as in (4) above the net change due to the practice is approximately

$$q^2 (1-w_m c_m) - q^2 + 2q^3 s_{aa} \doteq -q^2 w_m c_m$$

(ii) Gene frequency The approximate frequency of a in the parental generation is $q - s_{aa}q^2$.

The reduction in gene frequency due to selection against affected

individuals born is approximately $s_{aa}q^2 (1-w_m c_m)$

The reduction in gene frequency due to selective abortion of affected individuals is approximately $\frac{1}{4}. 4p^2q^2 w_m c_m \doteq q^2 w_m c_m$

To compensate for individuals aborted there are an additional $q^2 w_m c_m$ offspring born. Two-thirds of these are heterozygotes half of whose genes are a. Therefore the approximate increase in gene frequency as a result of reproductive compensation is $\frac{2}{3}. \frac{1}{2}. q^2 w_m c_m$

$= \frac{1}{3} q^2 w_m c_m$

Following the same reasoning as in (4) above the net change due to the practice is approximately $-s_{aa}q^2 (1-w_m c_m) - q^2 w_m c_m + \frac{1}{3} q^2 w_m c_m + q^2 s_{aa}$

$= q^2 w_m c_m (s_{aa} - \frac{2}{3})$

2a) AD diseases with complete penetrance

Improved treatment (1)

Suppose an improved treatment for the disease reduces selection against affected individuals by an amount s'_{A-}. The changes in disease incidence and gene frequency can be calculated by the same method as used in section (A) substituting $(s_{A-} - s'_{A-})$ for s_{A-}

(i) Disease incidence The change in disease incidence between parental and offspring generations is $-2q (s_{A-} - s'_{A-})$. Subtracting the effect of natural selection alone the net change due to the practice is $2qs'_{A-}$

(ii) Gene frequency Similarly the approximate change in gene frequency between parental and offspring generations is

$-(s_{A-} - s'_{A-}) q (1 - s_{A-} + s'_{A-})$

Subtracting the effect of natural selection alone the approximate net change in frequency due to the practice is

$$qs'_{A-}\ (1+s'_{A-}-2s_{A-})$$

If s_{A-} is large and s'_{A-} is small this net change is negative. This implies that there is a greater reduction in gene frequency after the introduction of an improved treatment, when the change is measured between the parental generation at reproduction and the offspring generation at reproduction. This is the result of the fact that with an improved treatment the gene frequency in the parental generation is higher than with no such treatment. This difference is trivial for AR diseases but not for AD diseases. Without improved treatment the frequency is $q(1-s_{A-})$ and with improved treatment it is $q(1-s_{A-}+s'_{A-})$. Although the result obtained above is mathematically correct it is of more practical interest to compare the proportionate changes in the frequency of A between parental and offspring generations. Without improved treatment the proportionate change is $-s_{A-}q(1-s_{A-}) / q(1-s_{A-}) = -s_{A-}$. With improved treatment the proportionate change is $(-s_{A-}+s'_{A-})$. Therefore the net effect of improved treatment is to diminish the proportionate reduction in gene frequency by an amount s'_{A-}.

Family limitation by carriers (4)

- prospective

In the case of AD diseases with complete penetrance heterozygous carriers of the deleterious allele are all affected. Suppose a proportion w_{A-} of these individuals is ascertained prospectively and of these a proportion c_i reduce the number of offspring they would have

had subsequently by a proportion f'_{A-}. Affected individuals originally have a fitness of $(1-s_{A-})$ and this is reduced by a proportion $w_{A-}c_i f'_{A-}$. Couples at risk of having affected offspring have frequency and fitness as follows:-

Mating type	Frequency	Fitness	Proportions of offspring	
			Aa	aa
Aa x aa	$4p^3q$	$(1-s_{A-})(1-w_{A-}c_i f'_{A-})$	$\frac{1}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{1}{2}.\ 4p^3q\ (1-s_{A-})(1-w_{A-}c_i f'_{A-})$

$$\doteq 2q(1-s_{A-})(1-w_{A-}c_i f'_{A-})$$

The difference in disease incidence between parental and offspring generations is then approximately $2q(1-s_{A-})(1-w_{A-}c_i f'_{A-}) - 2pq$

Subtracting the effect of natural selection alone the net change due to the practice is approximately $-2qw_{A-}c_i f'_{A-}\ (1-s_{A-})$

(ii) Gene frequency The approximate frequency of A in the parental generation at reproduction is $q(1-s_{A-})$

The reduction in gene frequency due to family limitation is approximately $\frac{1}{2}.\ 2pq\ w_{A-}c_i f'_{A-}(1-s_{A-}) \doteq qw_{A-}c_i f'_{A-}(1-s_{A-})$

The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2}\ s_{A-}\ .2q(1-s_{A-})(1-w_{A-}c_i f'_{A-})$

$$= qs_{A-}(1-s_{A-})(1-w_{A-}c_i f'_{A-})$$

Subtracting the effect of natural selection alone the net change in gene frequency due to the practice is approximately

$$-qw_{A-}c_i f'_{A-}(1-s_{A-}) - qs_{A-}(1-s_{A-})(1-w_{A-}c_i f'_{A-}) + qs_{A-}(1-s_{A-}) = -qw_{A-}c_i f'_{A-}(1-s_{A-})^2$$

Selective abortion with reproductive compensation (3)

- prospective

Suppose a proportion w_m of couples where one partner is affected is ascertained prospectively and a proportion c_m of these practise selection abortion of affected fetuses with reproductive compensation. Couples where one partner is affected have frequencies as follows:-

	Frequency	Fitness	Proportions of offspring	
			Aa	aa
Practising selective abortion	$4p^3qw_mc_m$	$(1-s_{A-})$	0	1
Not practising selective abortion	$4p^3q(1-w_mc_m)$	$(1-s_{A-})$	$\frac{1}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{1}{2}.\ 4p^3q\ (1-w_mc_m)(1-s_{A-}) \doteq 2q\ (1-w_mc_m)(1-s_{A-})$ Following the same reasoning as in (4) above the approximate net change in disease incidence due to the practice is $2q\ (1-w_mc_m)(1-s_{A-}) -2pq + 2qs_{A-}$ $\doteq -2qw_mc_m(1-s_{A-})$

(ii) Gene frequency The approximate frequency of A in the parental generation is $q(1-s_{A-})$. The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2}.\ s_{A-}.\ 2q(1-w_mc_m)(1-s_{A-}) \doteq qs_{A-}\ (1-w_mc_m)(1-s_{A-})$ The reduction in gene frequency due to selective abortion of affected individuals is approximately $\frac{1}{2}.\ \frac{1}{2}.\ 4p^3qw_mc_m\ (1-s_{A-}) \doteq q\ w_mc_m\ (1-s_{A-})$ There is no change in gene frequency as a result of the birth of additional offspring to compensate for those affected because none of them carry the A gene.

Therefore the net change in gene frequency due to the practice is approximately

$$-qs_{A-}(1-w_m c_m)(1-s_{A-}) - q\, w_m c_m (1-s_{A-}) + qs_{A-}(1-s_{A-}) = -q\, w_m c_m (1-s_{A-})^2$$

3) XR diseases

Improved treatment (1)

Suppose an improved treatment has the effect of reducing selection against aY males by an amount s'_a. The disease incidence and gene frequency changes can be calculated by the same method as used in section (A), substituting $(s_a - s'_a)$ for s_a.

(i) Disease incidence The change in disease incidence between parental and offspring generations is $-q^2(s_a - s'_a)$. Subtracting the effect of natural selection alone the net change due to the practice is approximately $q^2 s'_a$

(ii) Gene frequency The approximate change in gene frequency between parental and offspring generations is $-\frac{1}{3}q\,(s_a - s'_a)$.
Subtracting the effect of natural selection alone the approximate net change in gene frequency due to the practice is $\frac{1}{3}q\, s'_a$.

For XR diseases as for AD diseases there is an increased gene frequency in the parental generation when there is improved treatment and this increase is not trivial. Therefore it is more valid to compare the proportionate changes in the frequency of a. Without improved treatment the proportionate change in gene frequency is

$$-\tfrac{1}{3}q\, s_a \Big/ q(1-\tfrac{1}{3}s_a) = -s_a \Big/ (3-s_a)$$

With improved treatment the proportionate change is

$$-\frac{1}{3}q\ (s_a - s'_a) \Big/ q(1-\tfrac{1}{3}(s_a - s'_a)) = -(s_a - s'_a) \Big/ (3 - s_a + s'_a).$$

The net effect of improved treatment is therefore to reduce the proportionate reduction in gene frequency by an amount

$$\frac{-(s_a - s'_a)}{(3-s_a+s'_a)} + \frac{s_a}{(3-s_a)} = 3s'_a \Big/ (3-s_a)(3-s_a+s'_a)$$

Family limitation by carriers (4)

- prospective

Suppose a proportion w_{Aa} of carrier females is ascertained prospectively and of these a proportion c_i subsequently reduce their intended family size by a proportion f'_{Aa}. Since most carrier females are married to normal males the approximate changes in disease incidence and gene frequency are calculated by only considering couples of this type. These couples have frequency and fitness as shown:-

Mating type	Frequency	Fitness	Proportions of offspring			
			Females		Males	
			AA	Aa	AY	aY
Aa x AY	$2p^2q$	$(1-w_{Aa}c_i f'_{Aa})$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals amongst male offspring is $\frac{1}{2}.\ 2p^2q\ (1-w_{Aa}c_i f'_{Aa}) \doteq q(1-w_{Aa}c_i f'_{Aa})$ Subtracting the incidence in the parental generation and the effect of natural selection alone the approximate net change in disease incidence due to the practice is $-qw_{Aa}c_i f'_{Aa}$

(ii) Gene frequency The approximate frequency of a in the parental generation at reproduction is $q(1-\frac{1}{3}s_a)$

The approximate change in gene frequency due to family limitation by carrier females is $-\frac{2}{3}\ [\frac{1}{2}.\ 2pq\ w_{Aa}c_i f'_{Aa}] \doteq -\frac{2}{3}\ qw_{Aa}c_i f'_{Aa}$

The change in gene frequency due to selection against affected individuals born is approximately $-\frac{1}{3}s_a q\ (1-w_{Aa}c_i f'_{Aa})$

Therefore subtracting the effect of natural selection alone the approximate net change in gene frequency due to the practice is

$$-\frac{2}{3}qw_{Aa}c_i f'_{Aa} - \frac{1}{3}qs_a\ (1-w_{Aa}c_i f'_{Aa}) + \frac{1}{3}qs_a = -\frac{1}{3}qw_{Aa}c_i f'_{Aa}(2-s_a)$$

Selective abortion with reproductive compensation (3)

- prospective

Suppose a proportion w_m of couples where the female is a carrier is ascertained prospectively and a proportion c_m of these practise selective abortion of certain fetuses with reproductive compensation. The fetuses aborted may be:-

a) all males

b) affected males only

c) affected males and carrier females

Couples where the female is a carrier have frequencies as follows:-

	Frequency		Proportions of offspring			
			Females		Males	
			AA	Aa	AY	aY
Not practising selective abortion	$2p^2q(1-w_m c_m)$		$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$
Practising selective abortion	$2p^2q\ w_m c_m$	(a)	$\frac{1}{2}$	$\frac{1}{2}$	0	0
		(b)	$\frac{1}{2}$	$\frac{1}{2}$	1	0
		(c)	1	0	1	0

(i) Disease incidence In cases (a), (b) and (c) all affected individuals are aborted and so the change in disease incidence is the same in all of them. The approximate incidence of affected individuals amongst male offspring is $\frac{1}{2}.\ 2p^2q\ (1-w_m c_m) \doteq q(1-w_m c_m)$

Subtracting the incidence in the parental generation and the effect of natural selection alone the net change in disease incidence due to selective abortion is approximately $-qw_m c_m$

(ii) Gene frequency The approximate frequency of a in the parental generation at reproduction is $q(1-\frac{1}{3}s_a)$.

In (a), (b) and (c) there is the same reduction in gene frequency due to selection against affected individuals born and to selective abortion.

The reduction due to selection against affected individuals born is approximately $\frac{1}{3}qs_a(1-w_m c_m)$.

The reduction due to selective abortion is approximately $\frac{1}{3}[\frac{1}{2}.\ 2p^2 qw_m c_m]$
$\doteq \frac{1}{3}qw_m c_m$

(a) all males

To compensate for $2p^2 qw_m c_m$ males aborted there are an additional $2p^2 qw_m c_m$ females born. One half of these are carriers, half of their genes being a. Therefore the approximate change in gene frequency due to the birth of additional carrier females is $\frac{2}{3}[\frac{1}{2}.\ \frac{1}{2}.\ 2p^2 qw_m c_m]$
$\doteq \frac{1}{3}qw_m c_m$

Subtracting the effect of natural selection alone the net change in gene frequency due to selective abortion of all males is approximately
$-\frac{1}{3}qs_a(1-w_m c_m) - \frac{1}{3}qw_m c_m + \frac{1}{3}qw_m c_m + \frac{1}{3}qs_a = \frac{1}{3}qw_m c_m s_a$

(b) affected males

The number of fetuses aborted is only half that in (a) and there are only an additional $\frac{2}{3}p^2 qw_m c_m$ females born. By the same method as in (a) the approximate change in gene frequency due to the birth of additional carrier females is $\frac{1}{9}qw_m c_m$

The net change in gene frequency due to selective abortion of affected males is therefore approximately $-\frac{1}{3}qs_a(1-w_m c_m) - \frac{1}{3}qw_m c_m + \frac{1}{9}qw_m c_m + \frac{1}{3}qs_a$
$= \frac{1}{3}qw_m c_m(s_a - \frac{2}{3})$

(c) affected males and carrier females

In addition to affected males aborted there are $\frac{1}{2}.\ 2p^2qw_m c_m$ carrier females aborted.

The reduction in gene frequency due to abortion of carrier females is approximately $\frac{2}{3}[\frac{1}{2}.\ \frac{1}{2}.\ 2p^2qw_m c_m] \doteq \frac{1}{3}qw_m c_m$

The net change in gene frequency due to selective abortion of affected males and carrier females is therefore approximately

$-\frac{1}{3}qs_a(1-w_m c_m) - \frac{1}{3}qw_m c_m - \frac{1}{3}qw_m c_m + \frac{1}{3}qs_a = -\frac{1}{3}qw_m c_m(2-s_a)$

4) MF diseases

Improved treatment (1)

Suppose an improved treatment has the effect of reducing selection against affected individuals by an amount s_f'. The change in disease incidence can be calculated as in section (A) replacing s_f by $(s_f - s_f')$. The change in disease incidence between parental and offspring generations is approximately $-a^2p^2h^2(s_f - s_f')$.

Subtracting the effect of natural selection alone the net change due to the practice is approximately $a^2p^2h^2s_f'$

Family limitation by 'carriers' (4)

- prospective

Suppose it is possible to detect prospectively, individuals whose liability exceeds a certain value x' say where $x' \leq x$ (the abscissa at

the threshold). For example, for the disease diabetes mellitus individuals with a high blood sugar level may be ascertained. Suppose a proportion w_x is ascertained and of these a proportion c_i subsequently reduce their intended family size by a proportion f'_x. In the parental generation at birth individuals have the following frequencies and fitnesses:-

	Liability not greater than x'	Liability greater than x'	
Phenotype	Normal	Normal	Affected
Frequency	$1-P_x$	P_x-P	P
Mean liability	n_x	$\frac{a_x P_x - aP}{P_x - P}$	a
Fitness	1	$(1-w_x c_i f'_x)$	$(1-w_x c_i f'_x)(1-s_f)$

Following the method in section (A) the mean liability of the offspring can be shown to be $h^2 [w_x c_i f'_x (aPs_f - a_x P_x) - aPs_f]$. The difference in disease incidence between offspring and parental generations is approximately $z(=aP)$ times this difference in mean liability. Subtracting the effect of natural selection alone the net change due to the practice is approximately

$$-aP\, h^2 w_x c_i f'_x (a_x P_x - aPs_f)$$

Selective abortion with reproductive compensation (3)

- prospective

Suppose it is possible to detect prospectively couples where the mean liability of the two individuals exceeds a certain value x'' say.

Suppose P_x is the proportion of couples exceeding this liability and that a proportion w_x of them is ascertained and a proportion c_m

of these practise selective abortion with reproductive compensation. As calculated in section (A) if the fitness of affected individuals is $(1-s_f)$ and selection operates between the birth and reproduction of the parental generation the mean liability at reproduction is $[n(1-P) + aP(1-s_f)]$. This is therefore the mean liability of all couples and is approximately $-zs_f$ expressed as a deviation from the mean of the parents at birth. The distribution of liability of couples, after the removal of some individuals from the breeding population by selection, ~~is~~ may be regarded as approximately normal with variance one half that of individuals. Therefore the mean liability of couples whose liability exceeds x'', expressed in terms of the number of standard deviations of liability of individuals is, $\sqrt{2}\, a_x - zs_f$ (where a_x is the mean liability of these couples expressed in terms of the standard deviation of liability of couples). Similarly the mean liability of couples whose liability does not exceed x'' is $\sqrt{2}\, n_x - zs_f$.

This is summarised below:

	Liability not greater than x''	Liability greater than x''	
	No selective abortion	Selective abortion	No selective abortion
Frequency	$(1-P_x)$	$w_x c_m P_x$	$(1-w_x c_m)P_x$
Mean liability	$\sqrt{2}\, n_x - zs_f$	$\sqrt{2}\, a_x - zs_f$	$\sqrt{2}\, a_x - zs_f$

The mean liability of the offspring of couples not practising selective abortion is

$$h^2 \left[\frac{(1-P_x)(\sqrt{2}\, n_x - zs_f) + (1-w_x c_m) P_x (\sqrt{2}\, a_x - zs_f)}{(1-P_x) + (1-w_x c_m) P_x} \right]$$

substituting $n_x = \frac{-z_x}{1-P_x}$ and $a_x = \frac{z_x}{P_x}$ the mean liability becomes

$$h^2 \left[\frac{[-zs_f + w_x c_m (zs_f P_x - \sqrt{2}\, z_x)]}{1 - w_x c_m P_x} \right]$$

The proportion of the offspring of these couples who are affected is approximately $P + \frac{zh^2[-zs_f + w_x c_m (zs_f P_x - \sqrt{2}\, z_x)]}{1 - w_x c_m P_x}$

The offspring of these couples make up a proportion $(1 - w_x c_m P_x)$ of all offspring. Couples practising selective abortion have no affected offspring therefore the change in disease incidence between offspring and parental generations is approximately

$$P(1-w_x c_m P_x) + zh^2[-zs_f + w_x c_m (zs_f P_x - \sqrt{2}\, z_x)] - P$$

Subtracting the effect of natural selection alone the approximate net change in disease incidence due to the practice becomes

$$-w_x c_m P P_x [1 + ah^2(-aPs_f + \sqrt{2}\, a_x)]$$

TABLE 5.2

Possible net changes in disease incidence and gene frequency in autosomal recessive (AR) diseases with early onset ((a) and (b)).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	$2q^3 s'_{aa}$	$q^2 s'_{aa}$
2. Selection of mate	$-q^2 w_{Aa} c_i (2-w_{Aa} c_i)$	$q^2 s_{aa} w_{Aa} c_i (2-w_{Aa} c_i)$
3. Selective abortion with reproductive compensation		
- prospective	$-q^2 w_m c_m$	$q^2 w_m c_m (s_{aa} - \frac{2}{3})$
- retrospective	$-q^2 w_m c_m P_r$	$q^2 w_m c_m P_r (s_{aa} - \frac{2}{3})$
(B) Eugenic practices		
4. Family limitation by carriers	$-q^2 w_{Aa} c_i f'_{Aa} (2-w_{Aa} c_i f'_{Aa})$	$-q w_{Aa} c_i f'_{Aa}$
5. Family limitation by carriers at risk		
- prospective	$-q^2 w_m c_m f'_m$	$-q^2 w_m c_m f'_m (2-s_{aa})$
- retrospective	$-q^2 w_m c_m f'_m P_r$	$-q^2 w_m c_m f'_m P_r (2-s_{aa})$

TABLE 5.2 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$-\frac{8}{3} q^3 P_s w_{Aa} c_i f'_{Aa}$	$-\frac{4}{3} q^2 P_s w_{Aa} c_i f'_{Aa}$
7. Artificial insemination for spouses of carrier males	$-q^2 w_{Aa} c_i$	$-\frac{1}{2} q w_{Aa} c_i$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-q^2 w_m c_m$	$-q^2 w_m c_m (1-s_{aa})$
- retrospective	$-q^2 w_m c_m P_r$	$-q^2 w_m c_m P_r (1-s_{aa})$
9. Selective abortion without reproductive compensation		
- prospective	$-q^2 w_m c_m$	$-q^2 w_m c_m (1-s_{aa})$
- retrospective	$-q^2 w_m c_m P_r$	$-q^2 w_m c_m P_r (1-s_{aa})$

TABLE 5.3

Possible net changes in disease incidence and gene frequency in autosomal dominant (AD) diseases with complete penetrance with early onset ((a) and (b)).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	$2qs'_{A-}$	s'_{A-} **
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective	$-2qw_m c_m (1-s_{A-})$	$-qw_m c_m (1-s_{A-})^2$
- retrospective	$-2qw_m c_m P_r (1-s_{A-})$	$-qw_m c_m P_r (1-s_{A-})^2$
(B) Eugenic practices		
4. Family limitation by carriers	$-2qw_{A-} c_i f'_{A-} (1-s_{A-})$	$-qw_{A-} c_i f'_{A-} (1-s_{A-})^2$
5. Family limitation by carriers at risk		
- prospective	$-2qw_{A-} c_i f'_{A-} (1-s_{A-})$	$-qw_{A-} c_i f'_{A-} (1-s_{A-})^2$
- retrospective	$-2qw_{A-} c_i f'_{A-} P_r (1-s_{A-})$	$-qw_{A-} c_i f'_{A-} P_r (1-s_{A-})^2$

** proportionate change (see page 51)

TABLE 5.3 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	0	0
7. Artificial insemination for spouses of carrier males	$-qw_{A-}c_i(1-s_{A-})$	$-\frac{1}{2}qw_{A-}c_i(1-s_{A-})^2$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-qw_{A-}c_i(1-s_{A-})$	$-\frac{1}{2}qw_{A-}c_i(1-s_{A-})^2$
- retrospective	$-qw_{A-}c_i P_r(1-s_{A-})$	$-\frac{1}{2}qw_{A-}c_i P_r(1-s_{A-})^2$
9. Selective abortion without reproductive compensation		
- prospective	$-2qw_m c_m(1-s_{A-})$	$-qw_m c_m(1-s_{A-})^2$
- retrospective	$-2qw_m c_m P_r(1-s_{A-})$	$-qw_m c_m P_r(1-s_{A-})^2$

TABLE 5.4

Possible net changes in disease incidence and gene frequency in autosomal dominant (AD) diseases with incomplete penetrance with early onset ((a) and (b)).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	$2qy^2 s'_{A-}$	ys'_{A-} **
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective	$-2qy^2 w_m c_m (1-s_{A-})$	$-qy^2 w_m c_m \frac{(1-s_{A-})(1-2s_{A-}+ys_{A-})}{(2-y)}$
- retrospective	$-2qyw_m c_m P_r (1-ys_{A-})$	$-qyw_m c_m P_r \frac{(1-ys_{A-})(1-2s_{A-}+ys_{A-})}{(2-y)}$
(B) Eugenic practices		
4. Family limitation by carriers	$-2qy^2 w_{A-} c_i f'_{A-} (1-s_{A-})$	$-qyw_{A-} c_i f'_{A-} (1-s_{A-})(1-ys_{A-})$
5. Family limitation by carriers at risk		
- prospective	$-2qy^2 w_{A-} c_i f'_{A-} (1-s_{A-})$	$-qyw_{A-} c_i f'_{A-} (1-s_{A-})(1-ys_{A-})$
- retrospective	$-2qyw_{A-} c_i f'_{A-} P_r (1-ys_{A-})$	$-qw_{A-} c_i f'_{A-} P_r (1-ys_{A-})^2$

TABLE 5.4 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$\frac{-4qyP_s w_{A-} c_i f' (1-y)}{(2-y)}$	$\frac{-2qP_s w_{A-} c_i f' (1-y)(1-ys_{A-})}{2-y}$
7. Artificial insemination for spouses of carrier males	$-qy^2 w_{A-} c_i (1-s_{A-})$	$-\frac{1}{2}qyw_{A-} c_i (1-s_{A-})(1-ys_{A-})$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-qy^2 w_{A-} c_i (1-s_{A-})$	$-\frac{1}{2}qyw_{A-} c_i (1-s_{A-})(1-ys_{A-})$
- retrospective	$-qyw_{A-} c_i P_r (1-ys_{A-})$	$-\frac{1}{2}qw_{A-} c_i P_r (1-ys_{A-})^2$
9. Selective abortion without reproductive compensation		
- prospective	$-2qy^2 w_m c_m (1-s_{A-})$	$-qy^2 w_m c_m (1-s_{A-})^2$
- retrospective	$-2qyw_m c_m P_r (1-ys_{A-})$	$-qyw_m c_m P_r (1-ys_{A-})(1-s_{A-})$

TABLE 5.5

Possible net changes in disease incidence and gene frequency in X-linked recessive (XR) diseases (with early onset ((a) and (b)).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	$q^2 s'_a$	$3s'_a/(3-s_a)(3-s_a+s'_a)$**
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective		
a) all males	$-qw_m c_m$	$\frac{1}{3}qw_m c_m s_a$
b) affected males	$-qw_m c_m$	$\frac{1}{3}qw_m c_m (s_a - \frac{2}{3})$
c) affected males and carrier females	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m (2-s_a)$
- retrospective		
a) all males	$-qw_m c_m P_r$	$\frac{1}{3}qw_m c_m P_r s_a$
b) affected males	$-qw_m c_m P_r$	$\frac{1}{3}qw_m c_m P_r (s_a - \frac{2}{3})$
c) affected males and carrier females	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r (2-s_a)$
(B) Eugenic practices		
4. Family limitation by carriers	$-qw_{Aa} c_i f'_{Aa}$	$-\frac{1}{3}qw_{Aa} c_i f'_{Aa} (2-s_a)$
5. Family limitation by carriers at risk		
- prospective	$-qw_{Aa} c_i f'_{Aa}$	$-\frac{1}{3}qw_{Aa} c_i f'_{Aa} (2-s_a)$
- retrospective	$-qw_{Aa} c_i f'_{Aa} P_r$	$-\frac{1}{3}qw_{Aa} c_i f'_{Aa} P_r (2-s_a)$

** Proportionate change (see page 54)

TABLE 5.5 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$-\frac{2}{3}qP_s w_{Aa} c_i f'_{Aa}$	$-\frac{2}{9}qP_s w_{Aa} c_i f'_{Aa}(2-s_a)$
7. Artificial insemination for spouses of carrier males	0	$-\frac{1}{3}qw_a c_i(1-s_a)$
8. Artificial insemination for spouses of carrier males at risk	-	-
9. Selective abortion without reproductive compensation - prospective		
a) all males	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m(1-s_a)$
b) affected males	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m(1-s_a)$
c) affected males and carrier females	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m(2-s_a)$
- retrospective		
a) all males	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r(1-s_a)$
b) affected males	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r(1-s_a)$
c) affected males and carrier females	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r(2-s_a)$

TABLE 5.6

Possible net changes in disease incidence in multifactorial diseases with early onset ((a) and (b)).

Practice	Net change in disease incidence
(A) Dysgenic practices	
1. Improved treatment	$a^2P^2h^2s'_f$
2. Selection of mate	-
3. Selective abortion with reproductive compensation	
- prospective	$-w_x c_m P P_x [1+ah^2(\sqrt{2}a_x - aPs_f)]$
- retrospective	$-w_x c_m P_{rm} [P - a^2P^2h^2s_f]$
(B) Eugenic practices	
4. Family limitation by carriers	$-aPh^2 w_x c_x f'_x (a_x P_x - aPs_f)$
5. Family limitation by carriers at risk	
- prospective	$-aPh^2 w_x c_m f'_m [\sqrt{2}a_x P_x - aPP_x s_f]$
- retrospective	$-w_x c_m f'_m P_{rm} (P - a^2P^2h^2s_f)$
6. Family limitation by sibs of affected individuals	$-w_x c_x f'_x P_{sm} P(1+\frac{1}{4}h^4a^2)$
7. Artificial insemination for spouses of carrier males	-
8. Artificial insemination for spouses of carrier males at risk	-
9. Selective abortion without reproductive compensation	
- prospective	$-w_x c_m P P_x [1+ah^2(\sqrt{2}a_x - aPs_f)]$
- retrospective	$-w_x c_m P_{rm} (P - a^2P^2h^2s_f)$

TABLE 5.7

Possible net changes in disease incidence and gene frequency in autosomal recessive (AR) diseases with late onset (c).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	0	0
2. Selection of mate	$-q^2 w_{Aa} c_i (2-w_{Aa} c_i)$	0
3. Selective abortion with reproductive compensation		
- prospective	$-q^2 w_m c_m$	$-\frac{2}{3} q^2 w_m c_m$
- retrospective	$-q^2 w_m c_m P_r$	$-\frac{2}{3} q^2 w_m c_m P_r$
(B) Eugenic practices		
4. Family limitation by carriers	$-q^2 w_{Aa} c_i f'_{Aa} (2-w_{Aa} c_i f'_{Aa})$	$-q w_{Aa} c_i f'_{Aa}$
5. Family limitation by carriers at risk		
- prospective	$-q^2 w_m c_m f'_m$	$-2q^2 w_m c_m f'_m$
- retrospective	$-q^2 w_m c_m f'_m P_r$	$-2q^2 w_m c_m f'_m P_r$

TABLE 5.7 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$-\frac{8}{3}q^3 P_s w_{Aa} c_i f'_{Aa}$	$-\frac{4}{3}q^2 P_s w_{Aa} c_i f'_{Aa}$
7. Artificial insemination for spouses of carrier males	$-q^2 w_{Aa} c_i$	$-\frac{1}{2}q w_{Aa} c_i$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-q^2 w_m c_m$	$-q^2 w_m c_m$
- retrospective	$-q^2 w_m c_m P_r$	$-q^2 w_m c_m P_r$
9. Selective abortion without reproductive compensation		
- prospective	$-q^2 w_m c_m$	$-q^2 w_m c_m$
- retrospective	$-q^2 w_m c_m P_r$	$-q^2 w_m c_m P_r$

TABLE 5.8

Possible net changes in disease incidence and gene frequency in autosomal dominant (AD) diseases with complete penetrance with late onset (c).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	0	0
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective	$-2qw_m c_m$	$-qw_m c_m$
- retrospective	$-2qw_m c_m P_r$	$-qw_m c_m P_r$
(B) Eugenic practices		
4. Family limitation by carriers	$-2qw_{A-} c_i f'_{A-}$	$-qw_{A-} c_i f'_{A-}$
5. Family limitation by carriers at risk		
- prospective	$-2qw_{A-} c_i f'_{A-}$	$-qw_{A-} c_i f'_{A-}$
- retrospective	$-2qw_{A-} c_i f'_{A-} P_r$	$-qw_{A-} c_i f'_{A-} P_r$
6. Family limitation by sibs of affected individuals	0	0
7. Artificial insemination for spouses of carrier males	$-qw_{A-} c_i$	$-\frac{1}{2}qw_{A-} c_i$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-qw_{A-} c_i$	$-\frac{1}{2}qw_{A-} c_i$
- retrospective	$-qw_{A-} c_i P_r$	$-\frac{1}{2}qw_{A-} c_i P_r$

TABLE 5.8 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
9. Selective abortion without reproductive compensation		
- prospective	$-2qw_m c_m$	$-qw_m c_m$
- retrospective	$-2qw_m c_m P_r$	$-qw_m c_m P_r$

TABLE 5.9

Possible net changes in disease incidence and gene frequency in autosomal dominant (AD) diseases with incomplete penetrance with late onset (c).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	0	0
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective	$-2qy^2 w_m c_m$	$-qy^2 w_m c_m/(2-y)$
- retrospective	$-2qyw_m c_m P_r$	$-qyw_m c_m P_r/(2-y)$
(B) Eugenic practices		
4. Family limitation by carriers	$-2qy^2 w_{A-} c_i f'_{A-}$	$-qyw_{A-} c_i f'_{A-}$
5. Family limitation by carriers at risk		
- prospective	$-2qy^2 w_{A-} c_i f'_{A-}$	$-qyw_{A-} c_i f'_{A-}$
- retrospective	$-2qyw_{A-} c_i f'_{A-} P_r$	$-qw_{A-} c_i f'_{A-} P_r$

TABLE 5.9 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$\frac{-4qyP_s w_{A-} c_i f'_{A-} (1-y)}{(2-y)}$	$\frac{-2qP_s w_{A-} c_i f'_{A-} (1-y)}{(2-y)}$
7. Artificial insemination for spouses of carrier males	$-qy^2 w_{A-} c_i$	$-\frac{1}{2}qyw_{A-} c_i$
8. Artificial insemination for spouses of carrier males at risk		
- prospective	$-qy^2 w_{A-} c_i$	$-\frac{1}{2}qyw_{A-} c_i$
- retrospective	$-qyw_{A-} c_i P_r$	$-\frac{1}{2}qw_{A-} c_i P_r$
9. Selective abortion without reproductive compensation		
- prospective	$-2qy^2 w_m c_m$	$-qy^2 w_m c_m$
- retrospective	$-2qyw_m c_m P_r$	$-qyw_m c_m P_r$

TABLE 5.10

Possible net changes in disease incidence and gene frequency in X-linked recessive (XR) diseases with late onset (c).

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	0	0
2. Selection of mate	-	-
3. Selective abortion with reproductive compensation		
- prospective		
a) all males	$-qw_m c_m$	0
b) affected males	$-qw_m c_m$	$-\frac{2}{9}qw_m c_m$
c) affected males and carrier females	$-qw_m c_m$	$-\frac{2}{3}qw_m c_m$
- retrospective		
a) all males	$-qw_m c_m P_r$	0
b) affected males	$-qw_m c_m P_r$	$-\frac{2}{9}qw_m c_m P_r$
c) affected males and carrier females	$-qw_m c_m P_r$	$-\frac{2}{3}qw_m c_m P_r$
(B) Eugenic practices		
4. Family limitation by carriers	$-qw_{Aa} c_i f'_{Aa}$	$-\frac{2}{3}qw_{Aa} c_i f'_{Aa}$
5. Family limitation by carriers at risk		
- prospective	$-qw_{Aa} c_i f'_{Aa}$	$-\frac{2}{3}qw_{Aa} c_i f'_{Aa}$
- retrospective	$-qw_{Aa} c_i f'_{Aa} P_r$	$-\frac{2}{3}qw_{Aa} c_i f'_{Aa} P_r$

TABLE 5.10 (contd.)

Practice	Net change in disease incidence	Net change in gene frequency
(B) Eugenic practices		
6. Family limitation by sibs of affected individuals	$-\frac{2}{3}qP_s w_{Aa} c_i f'_{Aa}$	$-\frac{4}{9}qP_s w_{Aa} c_i f'_{Aa}$
7. Artificial insemination for spouses of carrier males	0	$-\frac{1}{3}qw_a c_i$
8. Artificial insemination for spouses of carrier males at risk	-	-
9. Selective abortion without reproductive compensation		
- prospective		
a) all males	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m$
b) affected males	$-qw_m c_m$	$-\frac{1}{3}qw_m c_m$
c) affected males and carrier females	$-qw_m c_m$	$-\frac{2}{3}qw_m c_m$
- retrospective		
a) all males	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r$
b) affected males	$-qw_m c_m P_r$	$-\frac{1}{3}qw_m c_m P_r$
c) affected males and carrier females	$-qw_m c_m P_r$	$-\frac{2}{3}qw_m c_m P_r$

TABLE 5.11

Possible net changes in disease incidence in multifactorial (MF) diseases with late onset (c).

Practice	Net change in disease incidence
(A) Dysgenic practices	
1. Improved treatment	0
2. Selection of mate	-
3. Selective abortion with reproductive compensation	
- prospective	$-w_x c_m PP_x(1+\sqrt{2}h^2 aa_x)$
- retrospective	$-w_x c_m PP_{rm}$
(B) Eugenic practices	
4. Family limitation by carriers	$-aPh^2 w_x c_x f'_x a_x P_x$
5. Family limitation by carriers at risk	
- prospective	$-\sqrt{2}aPh^2 w_x c_m f'_m a_x P_x$
- retrospective	$-w_x c_m f'_m P_{rm} P$
6. Family limitation by sibs of affected individuals	$-w_x c_x f'_x P_{sm} P(1+\frac{1}{2}h^4 a^2)$
7. Artificial insemination for spouses of carrier males	-
8. Artificial insemination for spouses of carrier males at risk	-
9. Selective abortion without reproductive compensation	
- prospective	$-w_x c_m PP_x(1+\sqrt{2}h^2 aa_x)$
- retrospective	$-w_x c_m PP'_{rm}$

(6) DISCUSSION OF RESULTS OBTAINED

In section (5) and in appendix (1) a large number of formulae are obtained for the changes in disease incidence and gene frequency resulting from various practices. The actual sizes of the changes depend on the values of parameters, such as gene frequency, which are independent of the practice being studied and on the values of parameters actually measuring the practice. They are also dependent upon the age at which the disease has its onset. In order to illustrate the effects of the different practices some examples of possible changes are plotted in Figures 6.1 - 6.15. These are the net changes in disease incidence and gene frequency for AR (without heterozygote advantage), AD, XR and MF diseases of early onset for given values of the parameters.

The net changes in disease incidence are expressed as percentages of the initial incidence (i.e. $\underline{q}^2$ for AR diseases, $2\underline{qy}$ for AD diseases, $\underline{q}$ for XR diseases and $\underline{P}$ for MF diseases). In the majority of cases the net changes in gene frequency are expressed as percentages of the initial frequency $\underline{q}$. For AD and XR diseases the net proportionate changes in gene frequency (multiplied by 100) resulting from improved treatments (see pages 51 and 54) are plotted in Figures 6.2, 6.11 and 6.13. In Figure 6.9 the net change in frequency of an AR gene is expressed as a percentage of $\underline{q}^2$. This is because most of the changes in frequency of an AR gene are proportional to $\underline{q}^2$. With two exceptions therefore the values plotted in Figure 6.9 are valid for all values of $\underline{q}$. The measurement along the abscissa depends on the particular practice being considered. For improved treatment it is the change in the fitness of affected individuals. For family limitation by certain individuals or couples the measurement is the product of the

proportion of individuals (couples) ascertained, the proportion of these adopting the practice and the proportionate change in fertility of those adopting the practice. It is therefore a measure of the proportionate change in fertility of all individuals or couples of the genotypes considered. For selection of mate, AI and selective abortion the measurement along the abscissa is the product of the proportion of individuals (couples) ascertained and the proportion of these who adopt the practice.

In Figures 6.1-6.7 changes for one particular practice for diseases of different modes of inheritance are given. The effect of a practice may be very different for two diseases with different modes of inheritance. The effects of all relevant practices for diseases of one mode of inheritance are plotted in Figures 6.8-6.15. These latter graphs illustrate the relative importance of the different practices in causing changes for diseases of each mode of inheritance studied. They can also be used to estimate the effects of several practices operating simultaneously.

Parameters independent of the practice considered

In this section the values used for each of the parameters are discussed, firstly for unifactorial diseases and then for multifactorial (MF) diseases.

Unifactorial diseases

i) Gene frequency (q)

For AD diseases all the changes (expressed as described, page 62) are independent of the initial gene frequency. This is also true for XR diseases with one exception but not for AR diseases. In the cases where the changes are dependent on q it is necessary to substitute a value for q in the formulae. For AR diseases the value of q used is 0.02. This is the approximate frequency of the gene for cystic fibrosis in Britain. This disease has a relatively high frequency when compared with other AR diseases and for many AR diseases the changes would be smaller than those calculated for this value of q. For XR diseases the value of q is 0.0001 as for haemophilia in Britain (Cavalli-Sforza & Bodmer (1971)). In the figures the curves where these values of q are used are marked with an asterisk (*). This shows that in these cases the changes plotted are evaluated for these specified frequencies.

ii) Penetrance (y)

For AD diseases with incomplete penetrance the value of y used is 0.5. With this value for y the changes are expected to be intermediate between those for AD diseases with complete penetrance and those for AR diseases.

iii) Coefficient of selection (s_i)

The reproductive fitness of individuals with early onset genetic diseases is in general very low. Many of these diseases result in death in early childhood. Taking s_i equal to unity reduces many of the changes to zero. In order to include the effects of as many practices as possible in the figures, the value used for s_i is 0.9.

iv) Proportion of offspring of couples at risk born after the first affected child (P_r)

The proportion of offspring born after the first affected child in the family is dependent both on the probability that any child is affected and on the family size distribution in the population. Fraser (1973) has derived formulae to measure the resultant reduction in fertility, if couples have no more children after the birth of a child affected with an AR disease. This reduction in fertility is the same as the proportion of offspring born after the first affected child. Fraser's results can be extended to AD and XR diseases.

Consider first an AR disease

Couples at risk of having an affected child are mainly those where both partners are heterozygous, as explained earlier. One quarter of their offspring are affected.

Families of size s can be divided into two groups:

a) a proportion $(\frac{3}{4})^s$ has s normal children and no affected children

b) a proportion $1-(\frac{3}{4})^s$ has at least one affected child

The mean number of affected children per couple is $s/4$

The mean number of first cases per couple is $1-(\frac{3}{4})^s$

Therefore for families of size s the proportion of affected offspring who are born after the first affected child (i.e. not first cases) is

$$\frac{\frac{s}{4} - [1-(\frac{3}{4})^s]}{\frac{s}{4}}$$

Summing over all family sizes, if F_s is the frequency of families of size s in the population, the proportion of affected offspring born after the first affected child is P_r where

$$P_r = \frac{\sum_{s=1}^{\infty} F_s \left[\frac{s}{4} - 1 + (\frac{3}{4})^s\right]}{\sum_{s=1}^{\infty} F_s \frac{s}{4}}$$

Since the chance that any child is affected is the same, whether they are born before or after the first affected child, P_r is also the proportion of all offspring born after the first affected child.

This result can be extended to diseases with other modes of inheritance. In general if p is the probability of having an affected child

$$P_r = \frac{\sum_{s=1}^{\infty} F_s \left[ps-1 + (1-p)^s\right]}{\sum_{s=1}^{\infty} F_s ps}$$

For AD diseases a proportion y/2 of the offspring of couples at risk (Aa x aa) is affected. Therefore p = 1/2 for diseases with complete penetrance and p = y/2 for diseases with incomplete penetrance. For XR diseases a quarter of the offspring of couples at risk (Aa x AY) are affected therefore p = 1/4. Substituting in these formulae values for F_s calculated from the British 1961 census (appendix 2) the values of P_r are as follows:-

AR diseases, AD diseases where y = 0.5 and XR diseases, $P_r \doteq 0.23$

AD diseases with complete penetrance, $P_r \doteq 0.38$

These values for P_r are used in Figures 6.1-6.13.

v) Proportion of the offspring of couples at risk who are normal sibs of affected individuals (P_s)

The proportion of the offspring who are normal sibs of affected individuals depends upon the family size distribution and on the proportion of offspring who are affected. Suppose couples at risk have a total of s offspring, r of whom are affected. If p is the probability that any child is affected the proportion of their offspring who are normal sibs of affected individuals is

$$\sum_{r=1}^{s} \binom{s}{r} p^r (1-p)^{s-r} \frac{(s-r)}{s}$$

Summing over all family sizes the proportion of offspring of couples at risk who are normal sibs of affected individuals is

$$P_s = \sum_{s=1}^{\infty} F_s \sum_{r=1}^{s} \binom{s}{r} p^r (1-p)^{s-r} \frac{(s-r)}{s}$$

Where F_s is the frequency of families of size s in the population.

For AR and XR diseases p = 1/4

For AD diseases with complete penetrance p = 1/2

For AD diseases with incomplete penetrance p = y/2

The values of P_s used in Figures 6.1-6.13 were obtained by substituting for F_s the same values as in (iv) above.

For AR and XR diseases and AD diseases where y = 0.5, $P_s \doteq 0.18$

For AD diseases with complete penetrance, $P_s \doteq 0.20$.

Multifactorial diseases

i) Initial incidence and heritability

Formulae for possible changes in incidence of an MF disease are given in Tables 5.6 and 5.11. There is no common factor by which each of these formulae can be multiplied, to obtain proportionate changes in disease incidence which are applicable to MF diseases in general. The changes are dependent not only on the initial disease incidence but also on the heritability. Two examples are presented in Figures 6.14 and 6.15. In Figure 6.14 changes in disease incidence are plotted for a disease with an initial incidence of 7.7 per thousand and heritability 0.6 (e.g. spina bifida and anencephaly in South Wales, Carter et al (1968)). In Figure 6.15 the changes refer to a disease with an incidence of 1.2 per thousand and heritability 0.76 (e.g. cleft lip with or without cleft palate in Utah, Woolf (1971)).

ii) Coefficient of selection s_f

For ease of calculation the fitness of affected individuals is taken to be zero ($s_f=1$) since it has only a slight effect on the changes in disease incidence.

iii) Proportion of affected individuals born after the first affected child in the family (P_{rm})

For unifactorial diseases it is possible to define a class of couples who are the parents of the majority of affected individuals (e.g. Aa x Aa couples in AR diseases). Since these couples all have the same probability of having an affected child it is possible, using this probability, to calculate the proportion of offspring of these

couples born after the first affected child. For MF diseases, however, the probability of having an affected child follows a continuous distribution and it is not possible to divide couples into discrete classes of those at risk and those not at risk of having an affected child. Because of the variable risk that any child is affected it is not possible to calculate a value for P_r as for unifactorial diseases. Instead, the proportion of all affected individuals who are further cases in affected sibships (P_{rm}), has been estimated for the diseases used as examples from the data given by Carter et al (1968) and Woolf (1971). In the study of Carter et al approximately five percent of index cases of spina bifida or anencephaly had an older sib affected with either disease. The authors estimate that ascertainment was 96 percent complete and so P_{rm} is taken to be approximately 0.05.

Woolf (1971) studied 496 propositi with cleft lip with or without cleft palate. From the figures given in his paper it can be calculated that approximately 5.8 percent of the propositi had an older brother or sister affected with the same condition. For this disease therefore P_{rm} can be taken to be approximately 0.058.

iv) Proportion of individuals who are normal sibs of affected individuals (P_{sm})

Approximate values for this parameter have been calculated from the data of Carter et al (1968) and Woolf (1971). The index patients in Carters study had a mean of 1.71 normal sibs. The value of P_{sm} is therefore approximately 1.71 times the disease incidence. This gives $P_{sm} = (1.71 \times 7.7)/1000 = 13.17/1000$. In Woolf's study family size was greater than in Carter's. In this case the mean number of normal sibs was approximately 3. This gives $P_{sm} = (3 \times 1.2)/1000 = 3.6/1000$.

Key to Figures 6.1-6.15 and 7.1-7.6

Symbol	Meaning
Diseases	
AR	Autosomal recessive
AD	Autosomal dominant with complete penetrance
AD^{+}	Autosomal dominant with penetrance 0.5
XR	X-linked recessive
Practices	
1	Improved treatment
2	Selection of mate
3	Selective abortion with reproductive compensation
4	Family limitation by carriers
5	Family limitation by carriers at risk
6	Family limitation by sibs of affected individuals
7	Artificial insemination for spouses of carrier males
8	Artificial insemination for spouses of carrier males at risk
9	Selective abortion without reproductive compensation
a	Selective abortion of all males
b	Selective abortion of affected males
c	Selective abortion of affected males and carrier females
p	Prospective detection
r	Retrospective detection
*	Evaluated for a specified frequency
**	Net proportionate change in gene frequency (x100)

The effect of a practice for diseases of different modes of inheritance

In this section the practices discussed in section (2) are considered in turn. The practices have effects on disease incidence and gene frequency which are dependent on the mode of inheritance of the disease. The different effects are shown in Figures 6.1-6.7.

(A) Dysgenic practices

1. Improved treatment

Possible effects of the introduction of treatments on disease incidence are shown in Figure 6.1. For all diseases there is an increase in incidence which is especially large for AD diseases as all the individuals whose fitness is improved are at risk of having an affected child. For AR and XR diseases the net increases are proportional to the initial gene frequency. In AR diseases where there is heterozygote advantage e.g. sickle cell anaemia in Africa the possible increase may be relatively large (Figure A3.1). In other AR and XR diseases where the gene frequencies are smaller the possible net increases in disease incidence are very small. This is because for recessive diseases individuals are only at risk of having an affected child in the unlikely event of their marrying a carrier of the allele. For XR diseases even if the fitness of affected individuals was increased to unity, the increase in disease incidence would only be of the order of 0.01 percent. This increase is too small to be shown accurately in Figure 6.1.

The corresponding changes in gene frequency are shown in Figure 6.2. In contrast to the increase in disease incidence the increase in

Figure 6.1 The effect on disease incidence of the introduction of improved treatments.

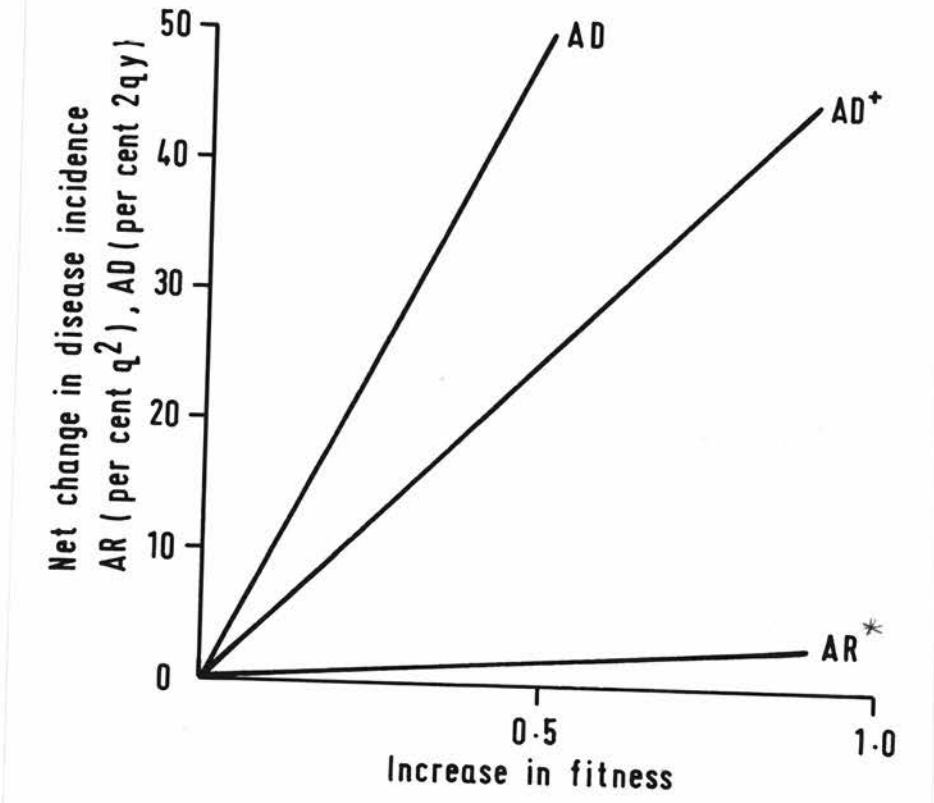
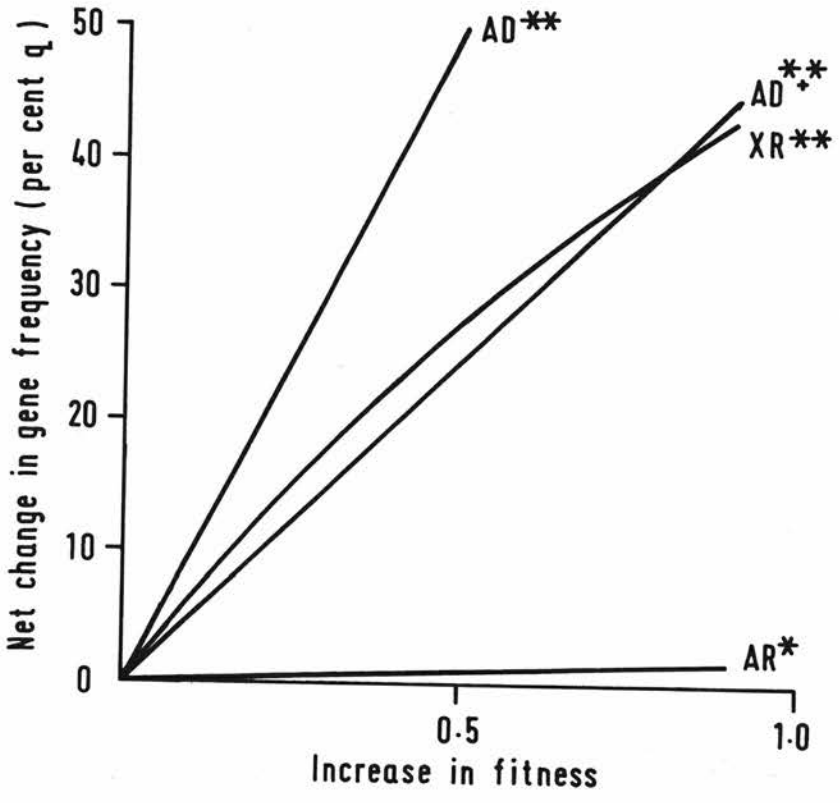

Net change in disease incidence
AR (per cent q^2), AD (per cent 2qy)
50
40
30
20
10
0
AD
AD+
AR*
0·5
1·0
Increase in fitness

Figure 6.2 The effect on gene frequency of the introduction of improved treatments.


50
40
30
20
10
0
Net change in gene frequency (per cent q)
AD**
AD**
XR**
AR*
0·5
1·0
Increase in fitness

frequency of deleterious XR alleles is relatively large. This is because one third of all the deleterious alleles are carried by affected individuals being passed on to carrier female offspring. For AR diseases the change in gene frequency is greater if there is heterozygote advantage (e.g. Figure A3.2) but in most AR diseases the change is small as only a proportion q of all deleterious alleles are carried by affected individuals. For AD diseases the net proportionate change in gene frequency is the same as the change in disease incidence.

2. Selection of mate

If heterozygous carriers of AR genes seek a homozygous normal partner there is a relatively large percentage decrease in disease incidence equal to that which occurs if the same proportion of carriers have no offspring (Figure 6.3). The percentage increase in gene frequency is slightly greater than that which occurs if there is an increase in fitness of affected individuals. The change is due solely to the decrease in the number of affected individuals born and the consequent reduction in the number of genes eliminated by selection. As discussed earlier, genes carried by affected individuals are only a very small proportion of the total and hence the gene frequency change is small.

3. Selective abortion with reproductive compensation

- prospective

The effect of selective abortion of the offspring of couples at risk of having an affected child is to produce a decrease in the disease incidence (Figure 6.3). For AR and XR diseases the net decrease is directly proportional to the proportion of couples adopting the

Figure 6.3 The effect on disease incidence of carrier detection, selective abortion and artificial insemination.

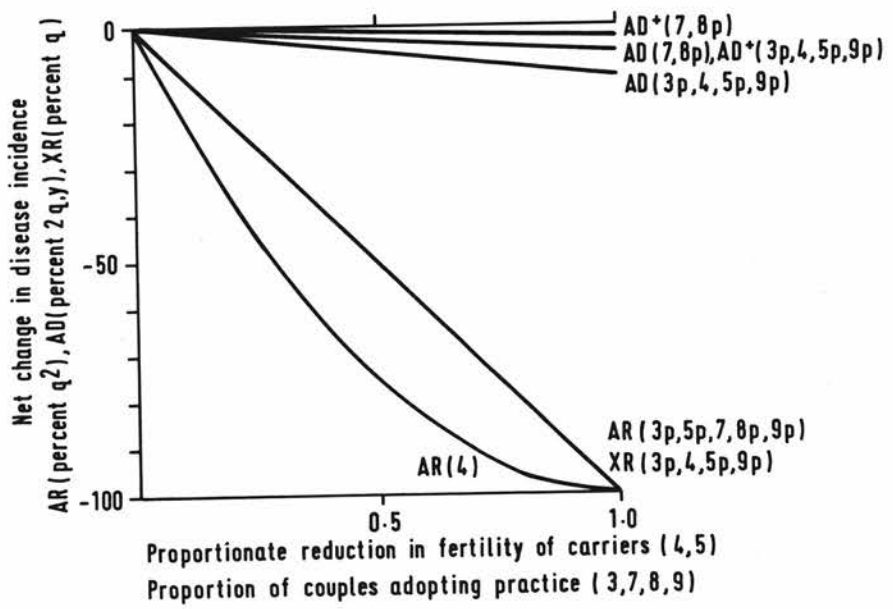
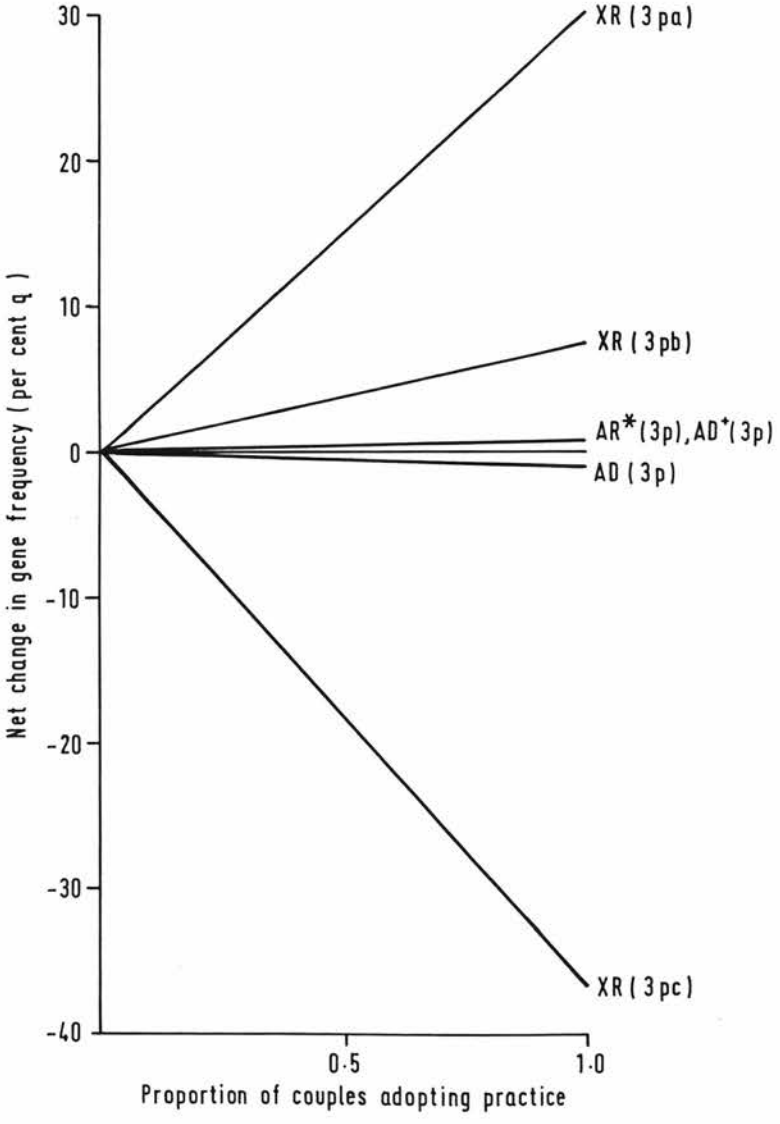

Net change in disease incidence
AR(percent q^2), AD(percent 2q,y), XR(percent q)
0
-50
-100
0·5
1·0
AD*(7,8p)
AD(7,8p),AD*(3p,4,5p,9p)
AD(3p,4,5p,9p)
AR(3p,5p,7,8p,9p)
XR(3p,4,5p,9p)
AR(4)
Proportionate reduction in fertility of carriers (4,5)
Proportion of couples adopting practice (3,7,8,9)

Figure 6.4 The effect on gene frequency of selective abortion with reproductive compensation.


30
20
10
0
-10
-20
-30
-40
Net change in gene frequency (per cent q)
XR (3 pα)
XR (3 pb)
AR* (3p), AD* (3p)
AD (3 p)
XR (3 pc)
0·5
1·0
Proportion of couples adopting practice

practice and in theory if all couples were to adopt the practice the disease could be completely eliminated. For AD diseases however the net decrease is much smaller as if affected individuals have low fitness they will not have many offspring who might be selectively aborted.

The net increase in gene frequency (Figure 6.4) is relatively large for XR diseases being greatest when all male fetuses are aborted, as if there is reproductive compensation, this is equivalent to replacing all affected males by carrier females. The increase is a quarter of this if only affected males are aborted. If affected males and carrier females are aborted there is a relatively large decrease in the frequency. For AR diseases the percentage increase in gene frequency is very small as the additional heterozygotes born are only a small proportion of the total, most being the offspring of one heterozygous and one homozygous normal parent. For AD diseases with complete penetrance there is always a decrease in gene frequency because none of the additional offspring born carry the deleterious allele.

- retrospective

The percentage changes in disease incidence and gene frequency are smaller if couples are not ascertained until they have had an affected child. The changes are equal to P_r times those which occur when ascertainment is prospective for AR and XR diseases and for AD diseases with complete penetrance. For the present British family size distribution P_r is quite small being approximately 0.23 for AR and XR diseases and approximately 0.38 for AD diseases with complete penetrance (see page 67). If family size were to become smaller P_r would be

reduced and hence the net changes would become even smaller. For example modifying the British family size distribution so that of all couples having one or more children one quarter have one child, one half have two children and one quarter have three children the corresponding values of P_r are 0.15 and 0.28.

For AD diseases with incomplete penetrance the theoretical changes calculated for retrospective detection may be greater than those for prospective detection. This is because the assumption is made that when detection is prospective only offspring of affected carriers are aborted, whereas when it is retrospective the offspring of a proportion of all carriers who have had an affected child are aborted. If affected individuals have low fitness the number of offspring of affected individuals may be smaller than the number of offspring born after an affected sib. For diseases where $y = 0.5$ retrospective detection has a theoretically greater effect on disease incidence and gene frequency if affected individuals have fitness less than 0.3.

B) Eugenic practices

4. Family limitation by carriers

The net changes in disease incidence resulting from family limitation by a proportion of all heterozygous carriers of the deleterious allele are shown in Figure 6.3. If there is a proportionate reduction in fertility of all carriers the net decrease in incidence of AD and XR diseases is the same as if an equal proportion practise selective abortion. The decrease in incidence of AR diseases is slightly greater as for a given proportion of all heterozygous carriers ascertained, a greater proportion of all heterozygous couples is ascertained.

The net decrease in gene frequency (Figure 6.5) is largest for AR and XR diseases where heterozygous carriers normally do not have a reduced fitness but is small for AD diseases.

5. Family limitation by carriers at risk

- prospective

For AD and XR diseases the net changes in disease incidence and gene frequency are the same as above. Family limitation by heterozygous couples in AR diseases produces a decrease in disease incidence directly proportional to the proportionate reduction in fertility of heterozygous couples (Figure 6.3). The gene frequency change (Figure 6.5) is much smaller as most heterozygous carriers are married to a homozygous normal individual but for diseases with heterozygote advantage the change may be greater (Figure A3.2).

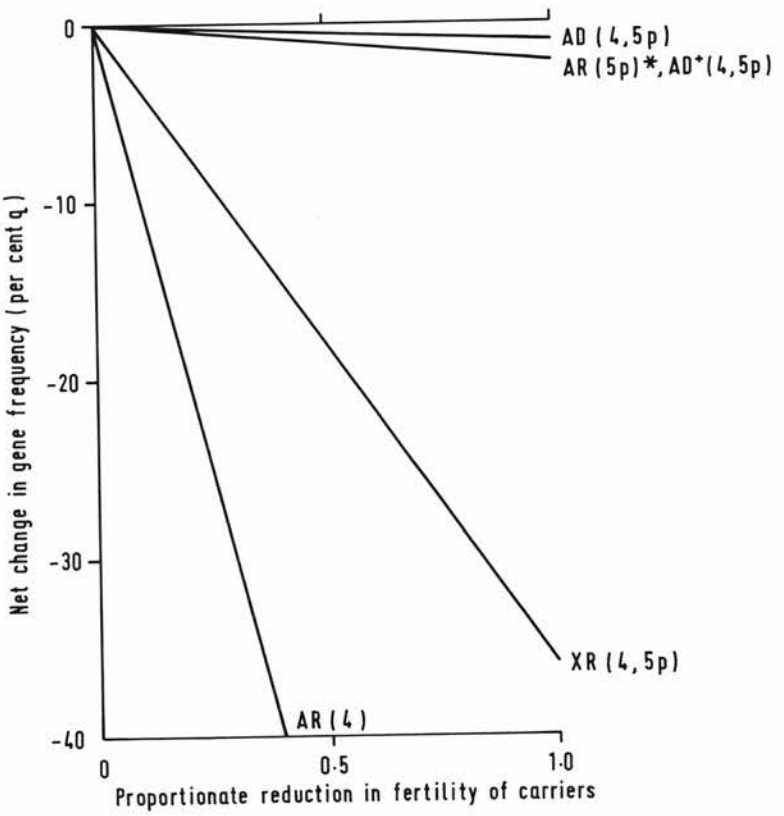
- retrospective

The changes in disease incidence and gene frequency differ from those when there is prospective ascertainment as described for selective abortion.

6. Family limitation by sibs of affected individuals

If sibs of individuals affected by AR, XR and AD diseases where there is incomplete penetrance have a reduced number of offspring there is a net decrease in disease incidence and in gene frequency in the next generation. The changes depend on the proportion of the offspring of couples at risk who are unaffected sibs of affected individuals (P_s). P_s in turn depends on the family size distribution. For the British family size distribution of the 1961 census $P_s = 0.18$ for AR and XR diseases and AD diseases where $y = 0.5$ (see page 67). If family size is smaller P_s is reduced though not to the same extent

Figure 6.5 The effect on gene frequency of family limitation by carriers.


0
-10
-20
-30
-40
Net change in gene frequency (per cent q)
AD (4,5p)
AR (5p)*, AD*(4,5p)
XR (4,5p)
AR (4)
0
0·5
1·0
Proportionate reduction in fertility of carriers

as P_r. This is because the size of P_r is determined by the number of offspring born after an affected child whereas P_s depends upon the number of children born before and after an affected child. For the example discussed under retrospective selective abortion (page 73) P_s becomes 0.15 for AR and XR diseases and AD diseases where y = 0.5.

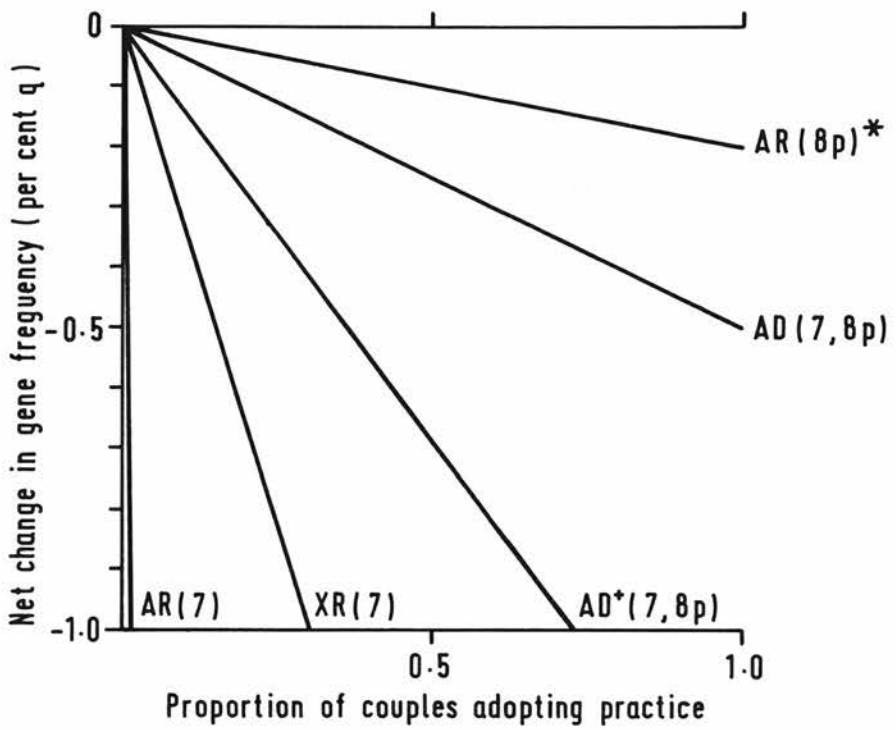
For AR diseases the net decreases in disease incidence and gene frequency are very small as most heterozygotes do not have affected sibs but are the offspring of one heterozygous and one homozygous normal parent. For AD diseases (where y = 0.5) and XR diseases the changes in disease incidence and gene frequency are larger. This is because all heterozygous carriers, not arising by new mutation or who are the offspring of normal females and affected males (in XR diseases), are the offspring of couples at risk and therefore might have affected sibs.

7. Artificial insemination for spouses of carrier males

Possible changes in disease incidence resulting from artificial insemination are shown in Figure 6.3. There is a net decrease in disease incidence which for AR diseases is the same as that when there is selective abortion. For AD diseases however the decrease is only one half that when there is selective abortion as AI is only applicable to half the couples at risk. In XR diseases AI has a negligable effect on the disease incidence as affected males are not at risk of having affected offspring unless married to a carrier female.

The net decrease in gene frequency is relatively large for AR diseases but much smaller for AD diseases where carrier males have low fitness (Figure 6.6). For XR diseases there is a decrease in the gene frequency intermediate between that for AD and AR diseases

Figure 6.6 The effect on gene frequency of artificial insemination.


0
-0·5
-1·0
Net change in gene freguency (per cent q)
AR (8p)*
AD (7, 8p)
AR (7)
XR (7)
AD* (7, 8p)
0·5
1·0
Proportion of couples adopting practice

caused by a reduction in births of carrier females.

8. Artificial insemination for spouses of carrier males at risk

- prospective

For AD diseases the net changes in disease incidence and gene frequency are the same as above since all carrier males are at risk. For XR diseases very few affected males are at risk so the effects are negligable. For AR diseases the decrease in disease incidence is the same as above but the decrease in gene frequency is smaller because most carrier males are married to a homozygous normal female.

- retrospective

The changes in disease incidence and gene frequency differ from those when there is prospective ascertainment as described for selective abortion.

9. Selective abortion without reproductive compensation

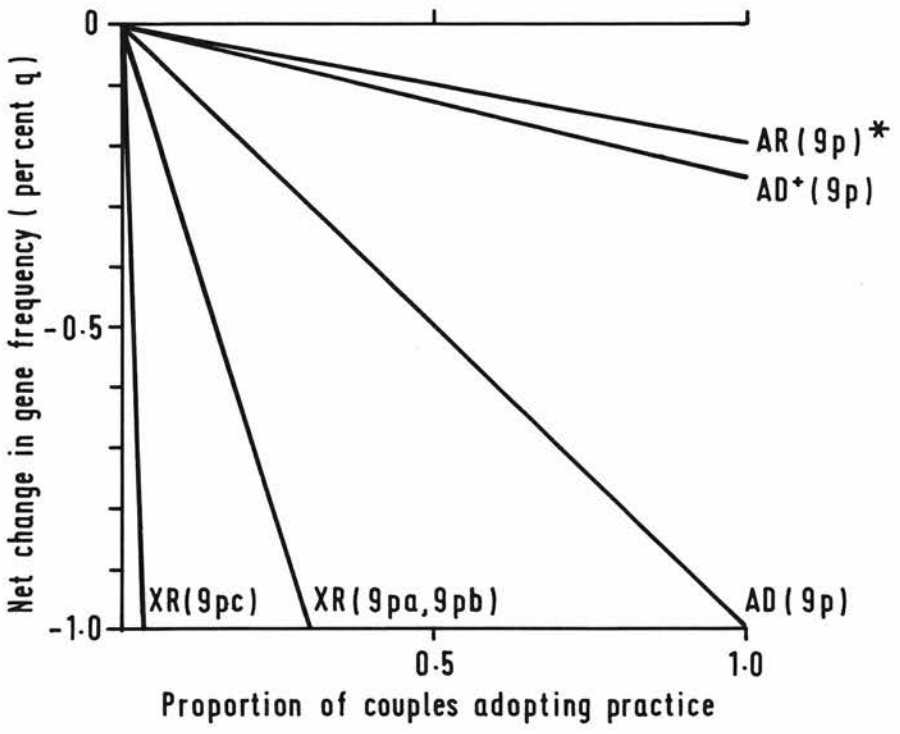
- prospective

There is a net decrease in disease incidence equal to that which occurs if there is reproductive compensation. The net decreases in gene frequency (Figure 6.7) are greatest for XR diseases in the case where there is selective abortion of both affected males and carrier females. If all or only affected males are aborted the change is about one tenth of this. For AD diseases with complete penetrance the changes are smaller if affected individuals have low fitness. In the case of AR diseases the gene frequency change is small because most of the deleterious alleles are borne by unaffected carriers.

- retrospective

The changes in disease incidence and gene frequency differ from those when there is prospective ascertainment as described for selective

Figure 6.7 The effect on gene frequency of selective abortion without reproductive compensation.


0
-0·5
-1·0
Net change in gene frequency (per cent q)
AR (9p)*
AD* (9p)
XR(9pc)
XR (9pa, 9pb)
AD (9p)
0·5
1·0
Proportion of couples adopting practice

abortion with reproductive compensation.

Diseases where affected individuals have greater fitness or the age of onset is greater

If affected individuals have fitness greater than in the above examples the net increases in disease incidence and gene frequency are smaller and the net decreases larger. The same is true for diseases with onset after the reproductive period if the parameters have the same value. However, as discussed earlier the changes are likely to be smaller in practice because fewer carriers would be ascertained.

Summary

The only practice considered which causes an increase in the disease incidence in the next generation is the introduction of improved treatments. This increase is small except for AD diseases and AR diseases where there is heterozygote advantage. All the other practices produce a decrease in the disease incidence. These decreases are small for AD diseases if carriers of the allele have low fitness, but potentially large for AR and XR diseases.

Increases in the gene frequency result from the introduction of improved treatments and also from selective abortion with reproductive compensation. For AD diseases the increase in gene frequency resulting from improved treatments is large but that resulting from selective abortion is small if carriers have low fitness. Relatively large increases in the frequency of XR genes result from both practices because additional carrier females are born but for AR diseases where there is no heterozygote advantage the increases are small because most deleterious alleles are transmitted to the next

generation by couples where only one partner is heterozygous.

Selective abortion without reproductive compensation, AI and family limitation by carriers all produce a net decrease in gene frequency which is largest for AR and XR diseases when a proportion of all heterozygous carriers reduce their family size.

If ascertainment is not until couples have had an affected child all the changes are smaller.

The effect of different practices for diseases of one mode of inheritance

1. Autosomal recessive diseases

The changes in disease incidence and gene frequency are plotted in Figures 6.8 and 6.9 respectively. It can be seen that the only practice which produces a net increase in disease incidence i.e. improved treatment, also produces the largest net increase in the gene frequency in one generation. Of the other practices which all produce a decrease in disease incidence, selection of mate and selective abortion with reproductive compensation are the only two which produce a net increase in gene frequency.

If a proportion of all heterozygous carriers either limit their family size or select a homozygous normal marriage partner there is a maximum decrease in disease incidence in one generation but the increase in gene frequency produced by selection of marriage partner gives a potential for increase in disease incidence in future generations. By contrast the reduction in gene frequency as a result of family limitation is considerably greater than any of the other changes and could produce a long term reduction in disease incidence. It is however likely, that only a small proportion of all carriers would restrict their family size. With family limitation by a proportion of carriers at risk the decrease in disease incidence is nearly as great as for family limitation by the same proportion of all carriers. The decrease in gene frequency, however, is much smaller when only carriers at risk are concerned, but the decrease is as large in size as any of the possible increases due to other practices. The difference between the effect on gene frequency of family limitation

by all carriers and by those at risk may be smaller when there is heterozygote advantage (see Figure A3.2).

Prospective detection of carrier couples with AI or selective abortion also results in the same decrease in disease incidence as above with small changes in the gene frequency. If ascertainment is retrospective both disease incidence and gene frequency changes are small.

The graphs can also be used to see what changes might result from combinations* of practices for diseases where there is no heterozygote advantage. For example, an increase in gene frequency resulting from an increase in reproductive fitness of affected individuals could be offset by a reduction in fertility of carriers. If there is a proportionate reduction in fertility of all carriers this reduction need only be about two percent of the change in reproductive fitness to prevent an increase in gene frequency. If only carriers at risk reduce their family size the proportionate reduction in fertility must be at least half the change in reproductive fitness. Similarly an increase in gene frequency if a proportion of all carriers were to select a homozygous normal mate could be offset by a voluntary reduction, of two percent of this proportion, in the fertility of all carriers. Retrospective detection of carrier couples with subsequent family limitation could offset an increase in the fitness of affected individuals of up to about 0.33.

After ascertainment couples at risk might either practise selective abortion of affected fetuses or reduce their family size. It can be seen that the gene frequency would not increase if the proportionate reduction in fertility was at least 20 percent of the proportion of

---

*For most combinations the joint effect is the sum of the individual effects. This is not the case when improved treatment is one of the practices (see appendix 4).

Figure 6.8 The effect of various practices on the incidence of an autosomal recessive disease.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7, 8, 9)

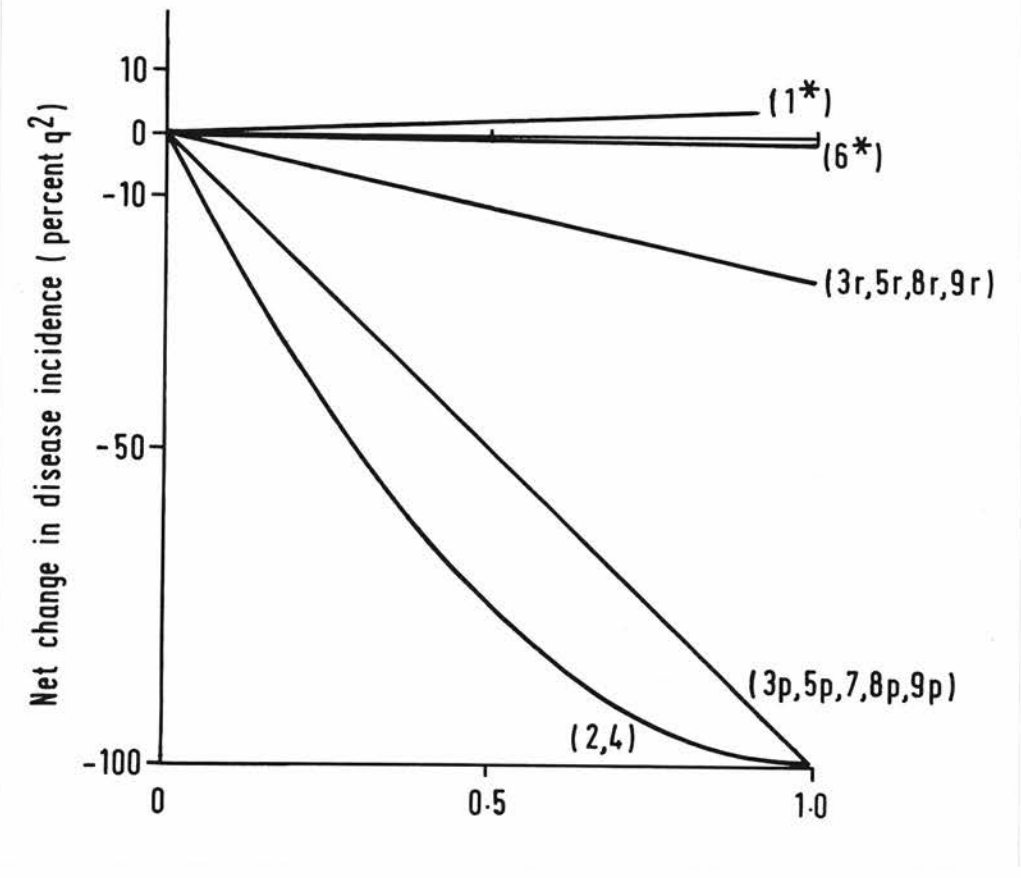

Net change in disease incidence (percent q^2)
10
0
-10
-50
-100
0
0·5
1·0
(1*)
(6*)
(3r,5r,8r,9r)
(3p,5p,7,8p,9p)
(2,4)

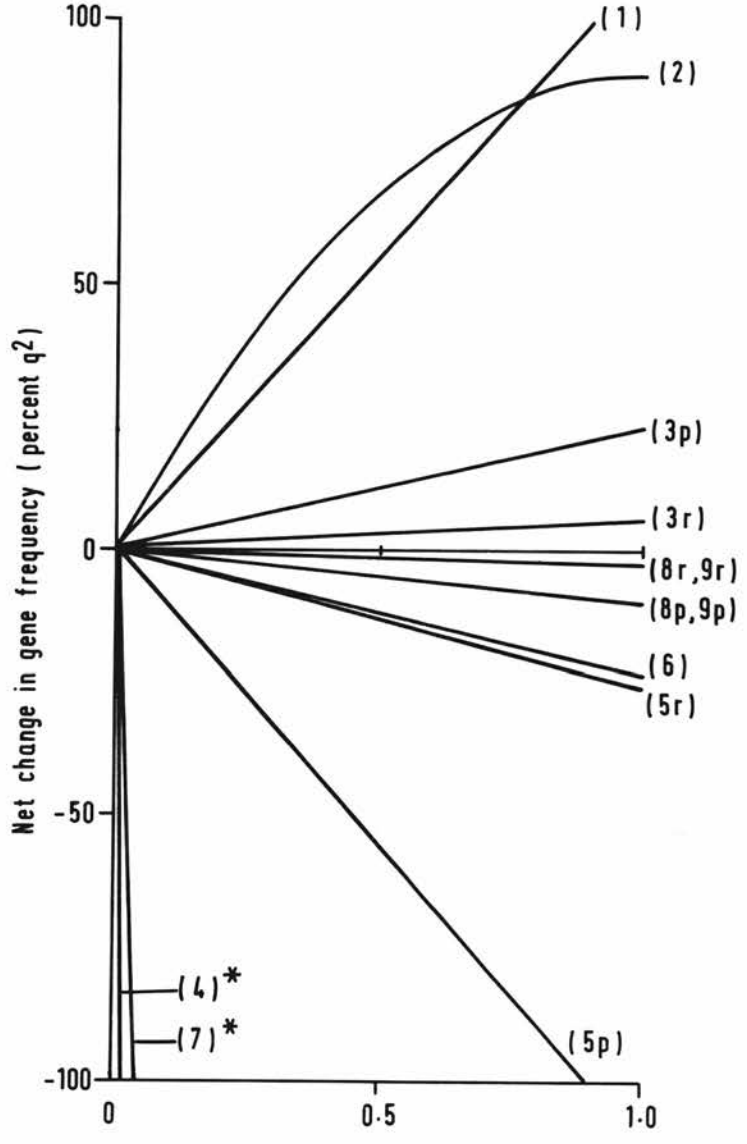
Figure 6.9 The effect of various practices on the frequency of an autosomal recessive gene.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7, 8, 9)


100
50
0
-50
-100
0
0·5
1·0
Net change in gene frequency (percent q^2)
(1)
(2)
(3p)
(3r)
(8r , 9r)
(8p , 9p)
(6)
(5r)
(4)*
(7)*
(5p)

couples practising selective abortion with reproductive compensation.

The effects of a large number of combinations of practices can be considered. If affected individuals have fitness of 0.1 as in this example the potential increases in gene frequency are smaller than the potential decreases. If the fitness was greater the increases would be even smaller and the decreases larger. For values of the fitness of more than 0.33 selective abortion with reproductive compensation would produce a decrease rather than an increase in gene frequency but for most diseases the fitness of affected individuals is very much lower than this.

Similarly the effect of combinations of practices can be estimated for sickle cell anaemia in Africa, where there is heterozygote advantage, from Figure A3.2. Compared with diseases where there is no heterozygote advantage a greater reduction in fertility would be required to offset the effect of improved treatment but a smaller reduction would be sufficient to offset the effect of mate selection.

2. Autosomal dominant diseases

The results for diseases of complete and incomplete penetrance are discussed together in this section, since the conclusions are very similar. Net changes in disease incidence for diseases where there is complete penetrance are shown in Figure 6.10. For diseases with a penetrance of 0.5 the changes in incidence are about half those for diseases with complete penetrance, except for retrospective ascertainment, as discussed earlier. The possible increase in incidence due to improved treatment is much larger than the possible decreases which result from all the other practices. This is because if the fitness of affected individuals is only 0.1 they have few offspring

anyway and the net effect of their practising family limitation or selective abortion is small.

Figure 6.11 shows the net changes in gene frequency for diseases with complete penetrance. The change resulting from an increase in the fitness of affected individuals is again very much greater than the others. For diseases where the penetrance is 0.5, though not when there is complete penetrance, selective abortion with reproductive compensation may cause an increase in the gene frequency. There is an increase if affected individuals have a fitness of less than one third and a decrease otherwise. All the other practices considered produce a net decrease in gene frequency. These changes, like those in disease incidence are very small, rising to a maximum of only one percent for diseases with complete penetrance where there is selective abortion or family limitation by carriers. For diseases with incomplete penetrance the maximum decrease of about seven percent occurs when there is retrospective family limitation.

The effects of practices acting in combination can best be seen from a consideration of the changes in disease incidence because all the changes are expressed as percentages of the same factor ($2q$). It can be seen from Figure 6.10 that the effect of increasing the fitness of affected individuals by 0.4 (from 0.1 to 0.5) by means of an improved treatment is to cause a net increase in disease incidence of 40 percent. This potential increase in disease incidence can only be offset if some of the treated individuals adopt one of the practices considered. The dotted lines show the net changes in disease incidence, resulting from other practices, if the fitness of affected individuals is 0.5, as it is after the introduction of the

Figure 6.10 The effect of various practices on the incidence of an autosomal dominant disease with complete penetrance.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5)

Proportion adopting practice (3, 7, 8, 9)

[solid lines, $s_i = 0.9$; dotted lines, $s_i = 0.5$]

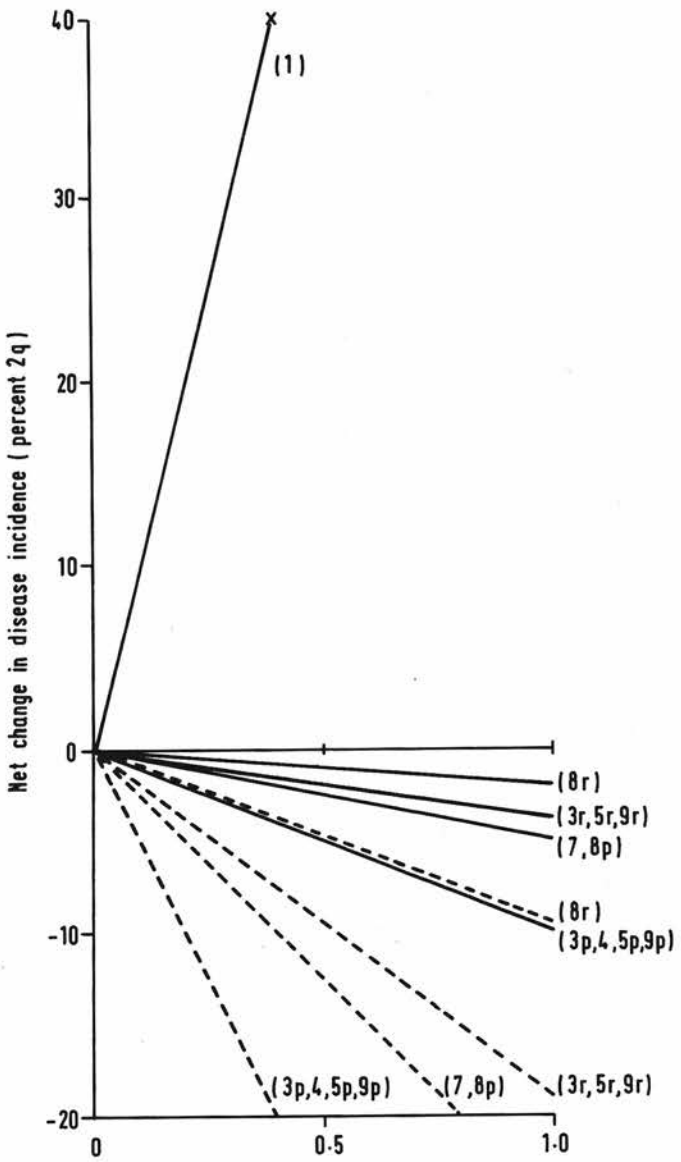

40
30
20
10
0
-10
-20
0
0·5
1·0
Net change in disease incidence (percent 2q)
(1)
(8r)
(3r,5r,9r)
(7,8p)
(8r)
(3p,4,5p,9p)
(3p,4,5p,9p)
(7,8p)
(3r,5r,9r)

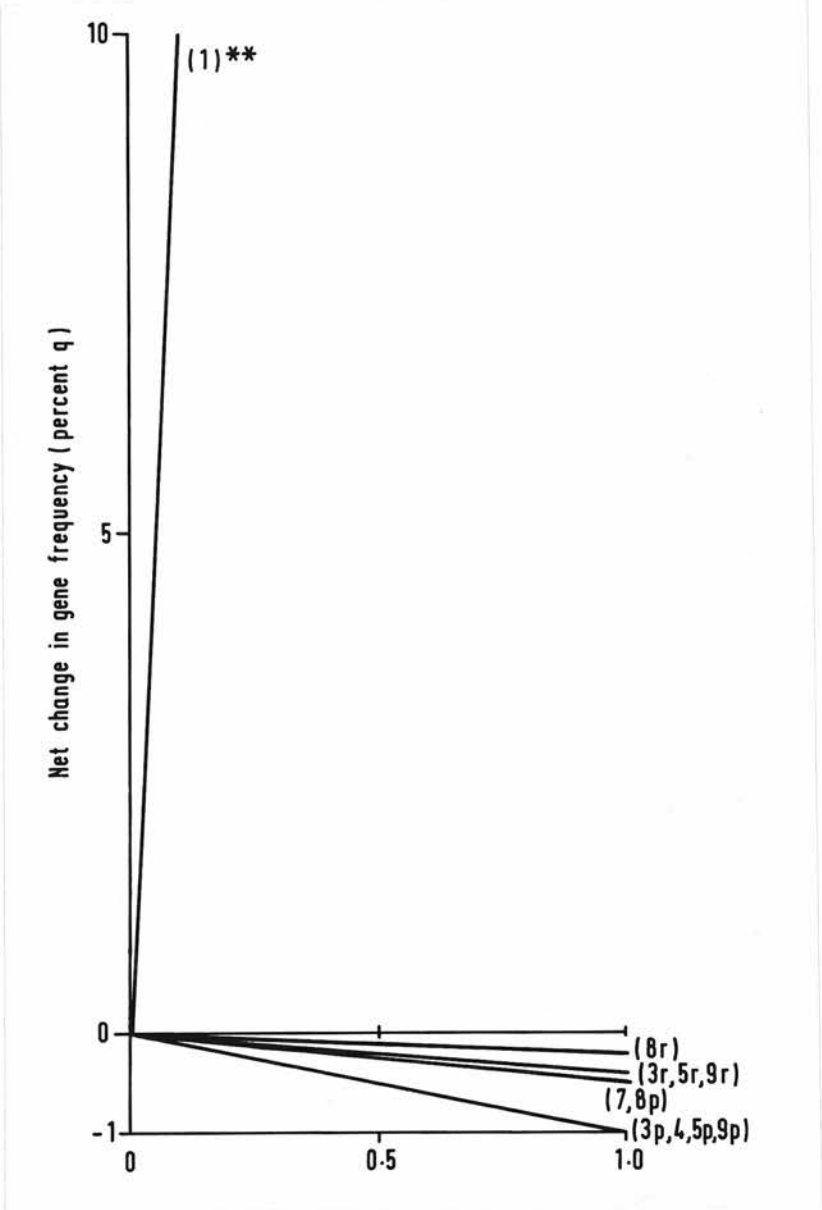
Figure 6.11 The effect of various practices on the frequency of an autosomal dominant gene with complete penetrance.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5)

Proportion adopting practice (3, 7, 8, 9)


10
5
0
-1
0
0·5
1·0
Net change in gene frequency (percent q)
(1)**
(8r)
(3r,5r,9r)
(7,8p)
(3p,4,5p,9p)

treatment. If the fitness of affected individuals was increased from 0.1 to 0.5 there would be an increase in the disease incidence in the next generation unless there was either a voluntary reduction in the fertility of all affected individuals by 80 percent or 80 percent of all affected individuals practised selective abortion of affected fetuses. If a proportion of spouses of affected males practised AI the net increase in disease incidence could be reduced to a minimum of 15 percent.

For AD diseases with a penetrance of 0.5 the same increase in the fitness of affected individuals would produce a net increase in disease incidence of about 20 percent. This could be offset if 80 percent of all affected individuals were to have no offspring or practised selective abortion of affected fetuses. If spouses of affected males practised AI this could reduce the net increase in disease incidence to a minimum of 7.5 percent.

In the same way, changes in disease incidence for other values of the fitness of affected individuals can be calculated. The effect of an increase of $\underline{x}$ in the fitness of affected individuals can only be offset if there is a voluntary reduction of $\underline{x}$ divided by the new fitness in the fertility of all affected individuals. Alternatively if this proportion ($\underline{x}$ divided by the new fitness) of affected individuals practised selective abortion of affected fetuses there would be no increase in the disease incidence. The effect of AI is to partially reduce the net increase in disease incidence.

3. X-linked recessive diseases

The percentage changes in the incidence of an XR disease are shown in Figure 6.12. The effect of improved treatments for affected

individuals is to produce a negligable increase in the disease incidence. Possible decreases in disease incidence are much greater however. If a proportion of carrier females were to have no offspring or to practise selective abortion of affected fetuses there would be an equal proportionate reduction in disease incidence.

In contrast to the change in disease incidence, the change in gene frequency after the introduction of improved treatments (Figure 6.13) is not negligable. The maximum proportionate increase if affected individuals have normal fitness is over 0.4. Of the other practices only selective abortion of all or affected males would produce an increase in gene frequency. The others would produce a decrease. A maximum net decrease in gene frequency of about 36 percent would result if carrier females had no offspring or practised selective abortion of both affected male and carrier female offspring. Decreases due to other practices are all less than 10 percent.

Changes caused by practices acting in combination* can also be derived from these graphs. If carrier females are ascertained at the same stage (prospectively or retrospectively) and decide either to have no offspring or to practise selective abortion of all or of affected males with reproductive compensation there is the same decrease in disease incidence no matter what are the relative proportions of females adopting the two practices. However with selective abortion of all males there is an increase in gene frequency unless the proportion having no offspring is more than 80 percent of that practising selective abortion. If only affected males are aborted

the corresponding value is 21 percent.

*For most combinations the joint effect is the sum of the individual effects. This is not the case when improved treatment is one of the practices (see appendix 4).

Figure 6.12 **The effect of various practices on the incidence of an x-linked recessive disease.**

Abscissa:-

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 9).

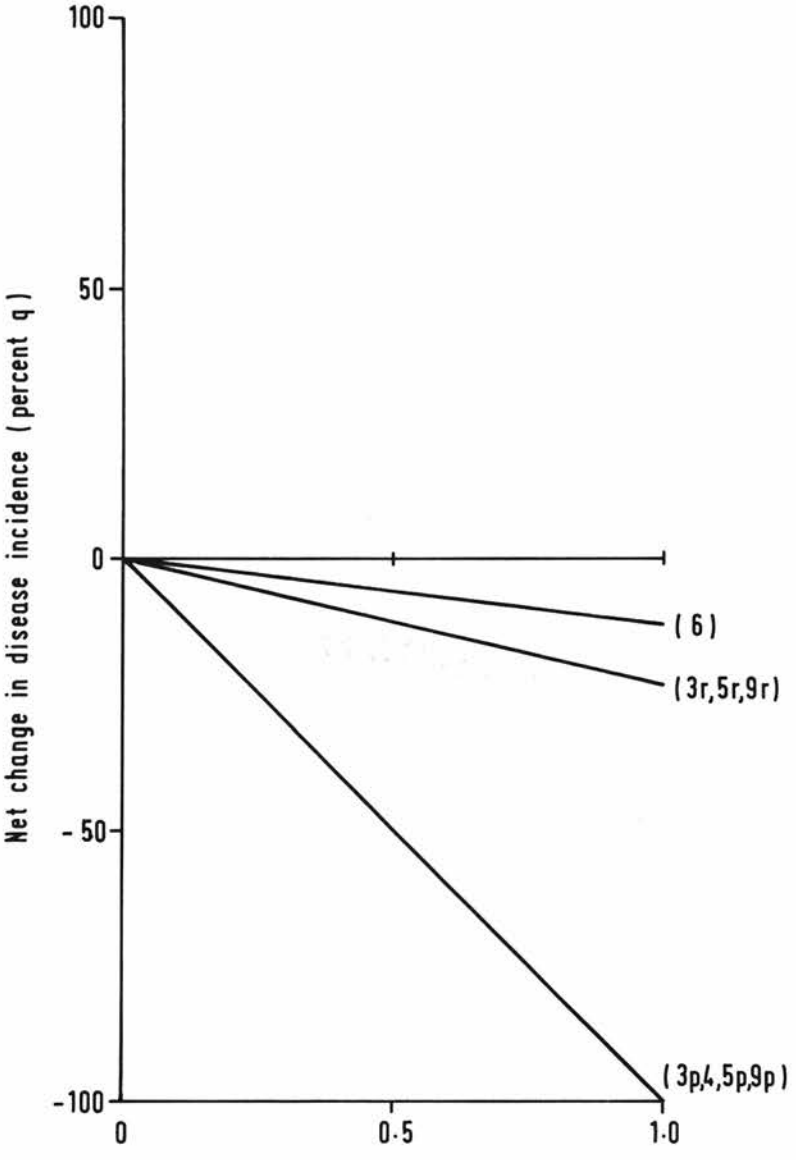

100
50
0
- 50
-100
0
0·5
1·0
Net change in disease incidence (percent q)
(6)
(3r,5r,9r)
(3p,4,5p,9p)

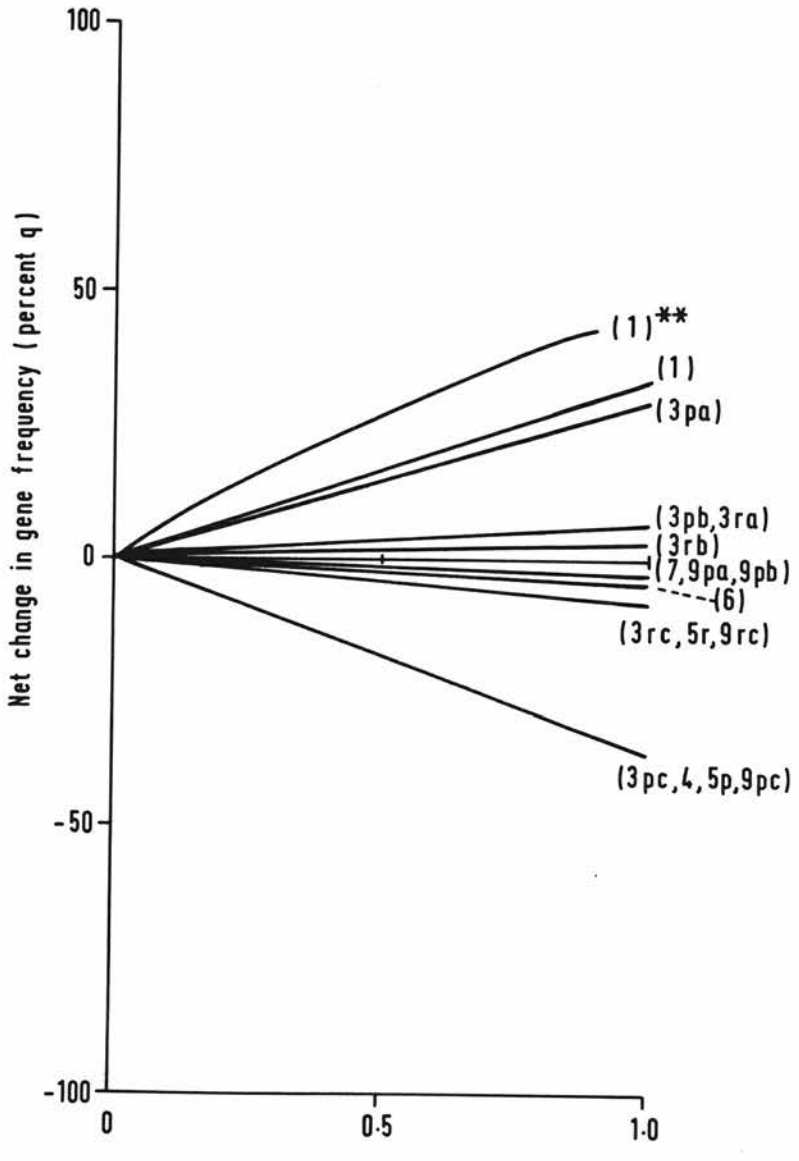
Figure 6.13 The effect of various practices on the frequency of an x-linked recessive gene.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 7, 9)


100
50
0
-50
-100
0
0·5
1·0
Net change in gene frequency (percent q)
(1)**
(1)
(3pa)
(3pb,3ra)
(3rb)
(7,9pa,9pb)
(6)
(3rc,5r,9rc)
(3pc,4,5p,9pc)

If a proportion of couples practise selective abortion some with reproductive compensation and some without reproductive compensation the net change in the gene frequency depends upon their relative proportions. With selective abortion of all or of affected males there is an increase in gene frequency unless the proportion practising reproductive compensation is less than 10 percent or 43 percent respectively of the proportion not practising reproductive compensation.

In Figure 6.13 the net change in gene frequency for improved treatments is given in addition to the net proportionate change. Consideration of the size of the former change shows that the effect of increasing the fitness of affected individuals by a certain amount can only be offset by a proportionate reduction of at least one half of this in the fertility of carrier females.

4. Multifactorial diseases

Possible changes in disease incidence for spina bifida and anencephaly (SBA) and for cleft lip with or without cleft palate (CLP) in the populations studied by Carter et al (1968) and Woolf (1971) are plotted in Figures 6.14 and 6.15 respectively. From the figures it can be seen that the introduction of improved treatments could increase the disease incidence by a maximum of about three percent for SBA and one percent for CLP. The other practices would all produce a net decrease in disease incidence. If couples were ascertained retrospectively and practised selective abortion or reduced their family size the disease incidence could be reduced by a maximum of about five percent. If sibs of affected individuals reduced their family size the reduction would only be of the order of one to two percent. Larger changes in disease incidence would only become possible if

individuals at high liability could be detected before they had any children (i.e. prospectively). The examples given in the figures are for the cases where individuals or couples in the upper 'five percent' and upper 'one percent' of the distribution of liability are ascertained.

As for AD diseases, in order to investigate the combined effect of improved treatments and the other practices, it is necessary to consider the effects of the other practices when the fitness of affected individuals is at its new higher level. This is because some of the individuals who may adopt the practice are affected. The dotted lines in Figures 6.14 and 6.15 show the changes in disease incidence if affected individuals have a fitness of unity as opposed to zero, for the case when there is family limitation by a proportion of all carriers. For all other practices producing a net decrease in disease incidence however, the change in incidence when affected individuals have normal fitness would be less than 0.5 percent greater than when their fitness is zero.

If the fitness of affected individuals was increased the resulting increase in disease incidence, in the next generation, could be offset if there was a voluntary reduction in fertility of couples after they had had an affected child. The minimum reduction in fertility needed would be 75 percent of the increase in fitness for SBA. For CLP the corresponding value is 20 percent.

Prospective detection of individuals at high liability with subsequent family limitation or selective abortion could also offset the effect of increased fitness of affected individuals. For example, for either SBA or CLP, a 20 percent reduction in the fertility of

Figure 6.14 The effect of various practices on the incidence of a multifactorial disease with prevalence 0.0077 and heritability 0.6 e.g. spina bifida and anencephaly.

Abscissa:-

Changes in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 9)

[solid lines, $s_f = 1$; dotted lines, $s_f = 0$]

† individuals in the upper five percent in the distribution of liability

‡ individuals in the upper one percent in the distribution of liability

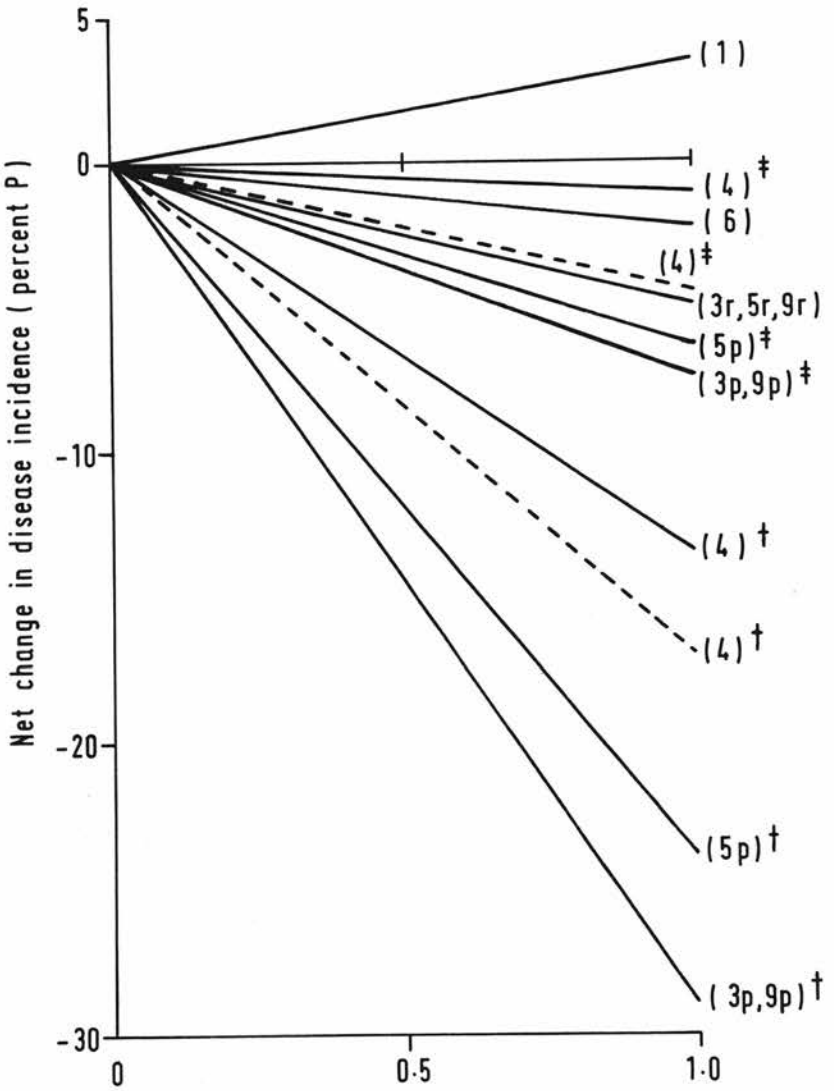

5
0
-10
-20
-30
Net change in disease incidence (percent P)
0
0·5
1·0
(1)
(4) ‡
(6)
(4) ‡
(3r,5r,9r)
(5p) ‡
(3p,9p) ‡
(4) †
(4) †
(5p) †
(3p,9p) †

Figure 6.15 The effect of various practices on the incidence of a multifactorial disease with prevalence 0.0012 and heritability 0.76 e.g. cleft lip with or without cleft palate.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 9)

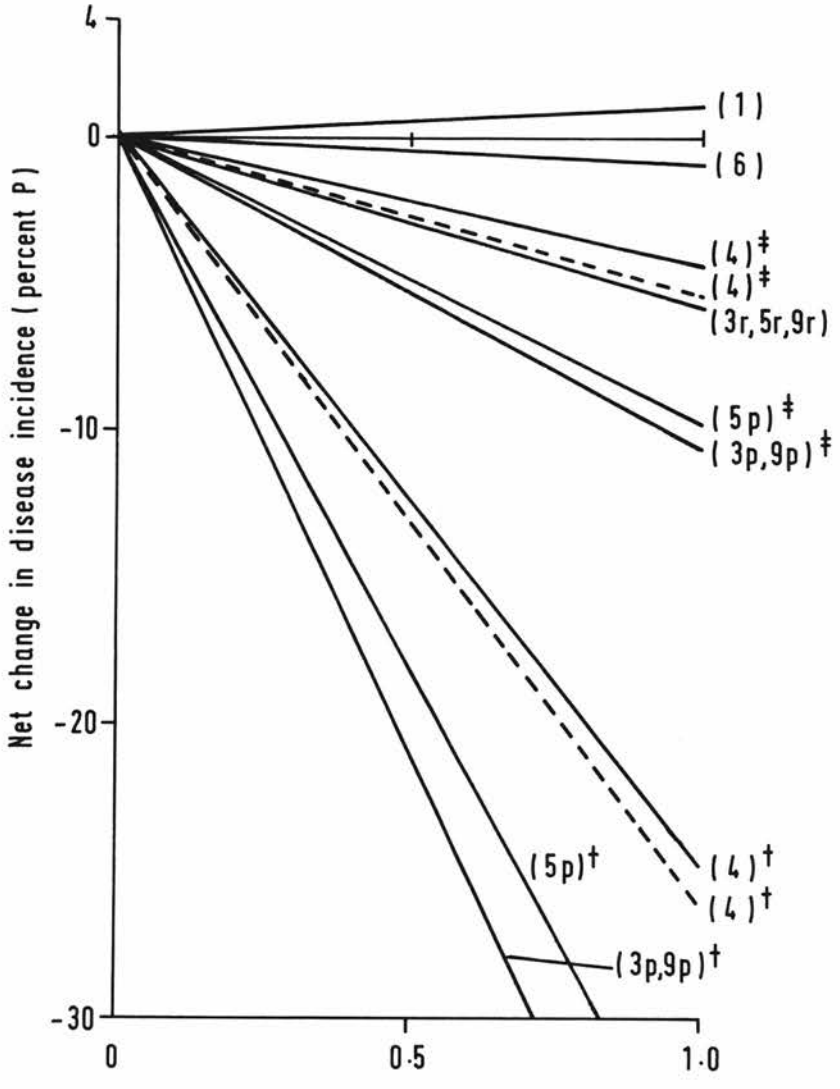
[solid lines, $s_f = 1$; dotted lines, $s_f = 0$]

† individuals in the upper five percent in the distribution of liability

‡ individuals in the upper one percent in the distribution of liability

Note

Selective abortion is not yet possible for this condition.


4
0
-10
-20
-30
0
0·5
1·0
Net change in disease incidence (percent P)
(1)
(6)
(4) ‡
(4) ‡
(3r, 5r, 9r)
(5 p) ‡
(3p, 9p) ‡
(4) †
(4) †
(5p) †
(3p, 9p) †

individuals in the upper 'one percent' of the distribution of liability could offset an increase in disease incidence resulting from an increase in the fitness of affected individuals to unity.

It must be emphasised that these results for SBA and CLP refer only to the populations studied by Carter *et al* (1968) and Woolf (1971). In other populations where the incidences of these diseases are different the proportionate changes in incidence may not be the same. In addition the changes which occur, if detection is retrospective or if relatives of affected individuals adopt one of the practices, are dependent on the family size distribution of the population. In general the changes in disease incidence are greater the greater is the initial incidence and the heritability though the latter has a negligable effect on the size of possible changes when couples are ascertained retrospectively.

Summary

For AR diseases where there is no heterozygote advantage possible net in increases in disease incidence are very small and decreases relatively large. The maximum increase is about four percent with improved treatment of affected individuals and the maximum decrease is 100 percent for family limitation by carriers or selection of mate. These maximum changes are however, most unlikely to be achieved in practice. With two exceptions all the net changes in gene frequency are very small and are directly proportional to q^2. In these two exceptions (namely family limitation by a proportion of all heterozygous carriers and AI for the spouses of a proportion of all heterozygous males), the net change in gene frequency is directly proportional to q. It can be calculated that a reduction of only two percent in

the fertility of carriers would be sufficient to offset an increase in gene frequency resulting from either an increase in the fitness of affected individuals to unity or the selection of a homozygous marriage partner by all heterozygotes. The changes calculated in appendix (3) suggest that for diseases where there is heterozygote advantage the main differences from the above are that improved treatment could produce larger increases in disease incidence and gene frequency and family limitation by heterozygous carriers could produce a greater decrease in gene frequency. In addition, to offset an increase in the fitness of affected individuals a greater reduction in the fertility of carriers would be required.

In the case of AD diseases, net changes in disease incidence and gene frequency due to improved treatments are very much larger than changes due to other practices. This is because in many disorders affected individuals have few offspring and so any further reduction of their fertility does not have very much additional effect. The possible increase in disease incidence as a result of improved treatments can only be offset if some of these individuals voluntarily have no offspring or practise selective abortion of affected fetuses. However if the treatment is very effective and affected individuals can lead a more or less normal life they might be less likely to adopt one of these practices.

As for AR diseases so in XR diseases possible increases in disease incidence are very small and decreases very great. The maximum increase in disease incidence in one generation is only of the order of 0.01 percent as very few affected males have affected offspring. By contrast the decrease, if carrier females reduce their family size or practise

selective abortion, reaches a theoretical maximum of 100 percent.

Although increases in disease incidence are negligable increases in gene frequency are not. An increase in the fitness of affected individuals or the selective abortion of all male offspring of carrier females with reproductive compensation could increase the gene frequency by up to about 30 percent. Decreases in frequency of the same size could result from family limitation or selective abortion of both affected male and carrier female fetuses. The overall change in gene frequency would therefore depend on the proportions of carrier females practising family limitation and selective abortion.

The changes in incidence of MF diseases depend on both the initial incidence and the heritability of the disease concerned. Improved treatments for affected individuals would have very little effect on the disease incidence because few affected individuals are offspring of an affected parent. If at the same time as an improved treatment was introduced a large enough proportion of couples who had had an affected child reduced their family size or practised selective abortion of affected fetuses there might be no overall increase in disease incidence. If it was possible to detect prospectively, individuals whose liability exceeded a certain value, the disease incidence might be reduced considerably.

(7) EXAMPLES TO ILLUSTRATE THE APPLICATION OF THE RESULTS

In order to illustrate the application of the results derived in the previous sections changes in disease incidence and gene frequency are calculated here for three diseases. The diseases considered are sickle cell anaemia, porphyria variegata and haemophilia with AR, AD and XR modes of inheritance respectively.

1. Sickle cell anaemia

Sickle cell anaemia has a high incidence in Blacks in the USA The incidence is approximately 25 in 10,000 and so the gene frequency is 0.05. This high incidence is the result of the fact that these Blacks are descendants of individuals who lived in areas of Africa where malaria was prevalent and there is good evidence that heterozygotes for the sickle cell gene have an increased resistance to malaria.

This disease has received much publicity recently in the USA where programs devised to reduce its incidence have been proposed (Culliton, 1972a,b). The formulae derived above can be used to estimate the changes in incidence of the condition which might thus be achieved. The results are plotted in Figure 7.1.

In the absence of any heterozygote advantage in the USA and with low fitness of affected individuals there will be a continuous elimination of deleterious alleles from the gene pool and a natural reduction in the incidence of the disease over time. In the figures the base lines are taken as lines corresponding to the present incidence of 25 in 10,000 and gene frequency of 0.05 and in order to obtain the new incidence and gene frequency this natural reduction must be added on to the changes due to the factors considered below.

i) Disease incidence

In the past affected individuals did not reproduce but now with the development of treatments, the fitness of affected individuals can be increased to about 0.33 (Cavalli-Sforza and Bodmer, 1971). The resulting net change in disease incidence can be calculated by substituting in formula A(1) in Table 5.2. The net change in incidence is $2q^3 s'_{aa} = 2(0.05)^3 0.33 = 0.825 \times 10^{-4}$.
The percentage change in incidence is $(2q^3 s'_{aa}/q^2) \times 100 = 3.3$.

Mass screening programs to detect carriers of the sickle cell gene have been initiated particularly amongst school children (Culliton, 1972b). If these individuals were subsequently to seek a marriage partner who was not also a carrier of the gene or if they were to limit their family size irrespective of the genotype of their marriage partner there could be quite a large reduction in the incidence of the disease. From Table 5.2 the net change in disease incidence as a result of family limitation by carriers is $-q^2 w_{Aa} c_i f'_{Aa} (2-w_{Aa} c_i f'_{Aa})$. If there was a five percent reduction in the fertility of all carriers the reduction in disease incidence would be $(0.05)^2 (0.05) (2-0.05) = 2.44 \times 10^{-4}$. The percentage reduction in incidence is $100(0.05) (2-0.05) = 9.75$.

Even if only those carriers whose marriage partner was also heterozygous were to limit their family size it can be calculated that there would still be a percentage reduction in the incidence of the condition equal to the percentage reduction in fertility of all heterozygous couples. This same reduction in incidence of the condition could be achieved if instead of limiting their family size this percentage of couples was to practise selective abortion of affected fetuses.

Figure 7.1 **Possible net changes in the incidence of sickle cell anaemia brought about by various practices, (I) as a percentage of the initial incidence, (II) actual change (x10,000), (relative to current practices).**

Abscissa:-

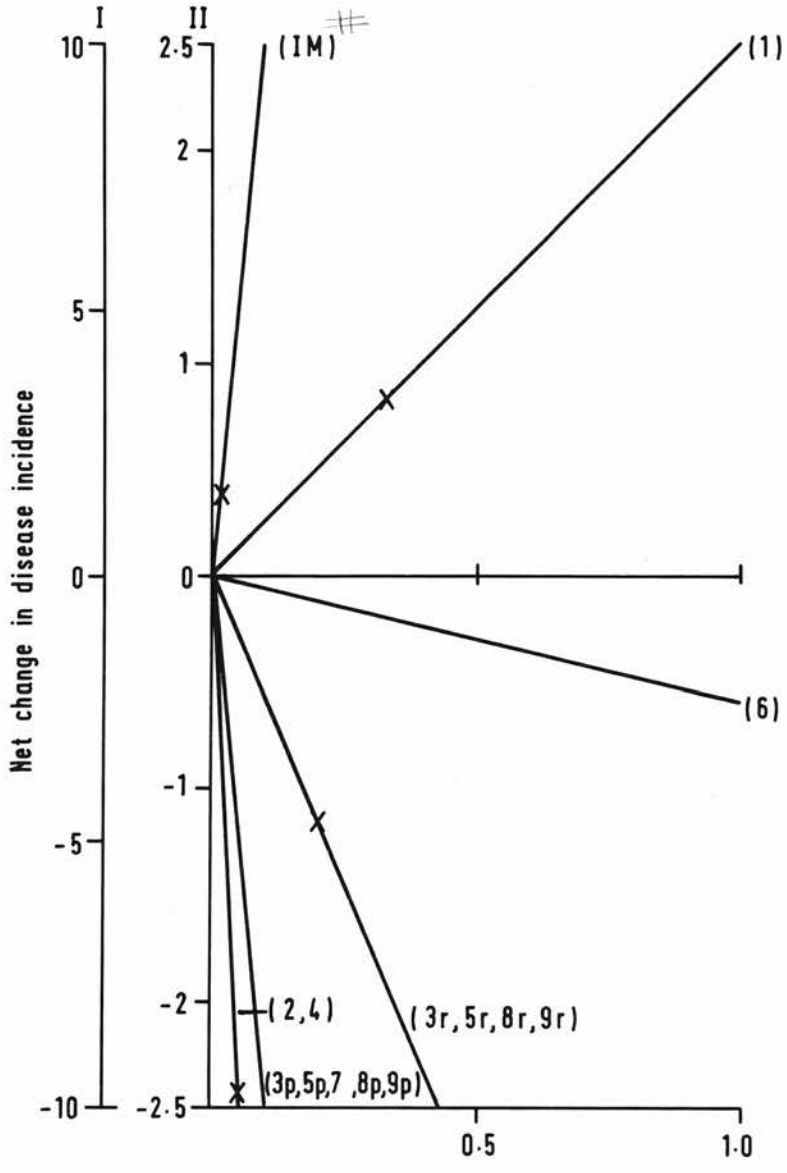
Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7, 8, 9)

Proportion of couples where one partner is Black and the other is White (IM)

The line labelled I.M. was drawn in error. The changes for this practice are identical to those for (3p, 5p, 7, 8p, 9p)


I
II
10
2·5
2
5
1
0
0
-1
-5
-2
-10
-2·5
0·5
1·0
Net change in disease incidence
(IM)
(1)
(6)
(2,4)
(3r, 5r, 8r, 9r)
(3p,5p,7 ,8p,9p)

Selective abortion for this condition is not possible at the moment but it seems likely to be possible in the near future (Hollenberg et al 1971). If family limitation or selective abortion were only initiated by couples after the birth of an affected child (i.e. retrospectively) the change in disease incidence would be smaller. From Table 5.2 the net reduction in disease incidence as a result of retrospective selective abortion is $q^2 w_m c_m P_r$. Taking the same value for P_r as used in section (6), if 20 percent of all affected fetuses conceived after the first affected individual in the family are selectively aborted the net change in disease incidence would be approximately $-(0.05)^2\ (0.2)\ (0.23) = -1.15 \times 10^{-4}$.

Similarly, changes in disease incidence resulting from other practices can be calculated from the formulae in Table 5.2. Although the disease has a high incidence amongst Blacks in the USA its incidence amongst Whites is small and intermarriage of Blacks and Whites could reduce its incidence quite substantially. However, it can be calculated from data given by Glick (1970) that at present only one to two percent of marriages of Black individuals are between couples where one partner is Black and the other is White. This would reduce the disease incidence only slightly as shown in Figure 7.1.

ii) Gene frequency

In addition to causing changes in the incidence of the condition the practices discussed above would cause changes in the gene frequency which would not always be in the same direction as the changes in disease incidence. There may therefore be a potential for an increase in the incidence of the disease in subsequent generations.

The changes in gene frequency are plotted in Figure 7.2. From

Figure 7.2 Possible net changes in the frequency of the sickle cell gene brought about by various practices, (I) as a percentage of the initial frequency, (II) actual change, (relative to current practices).

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7)

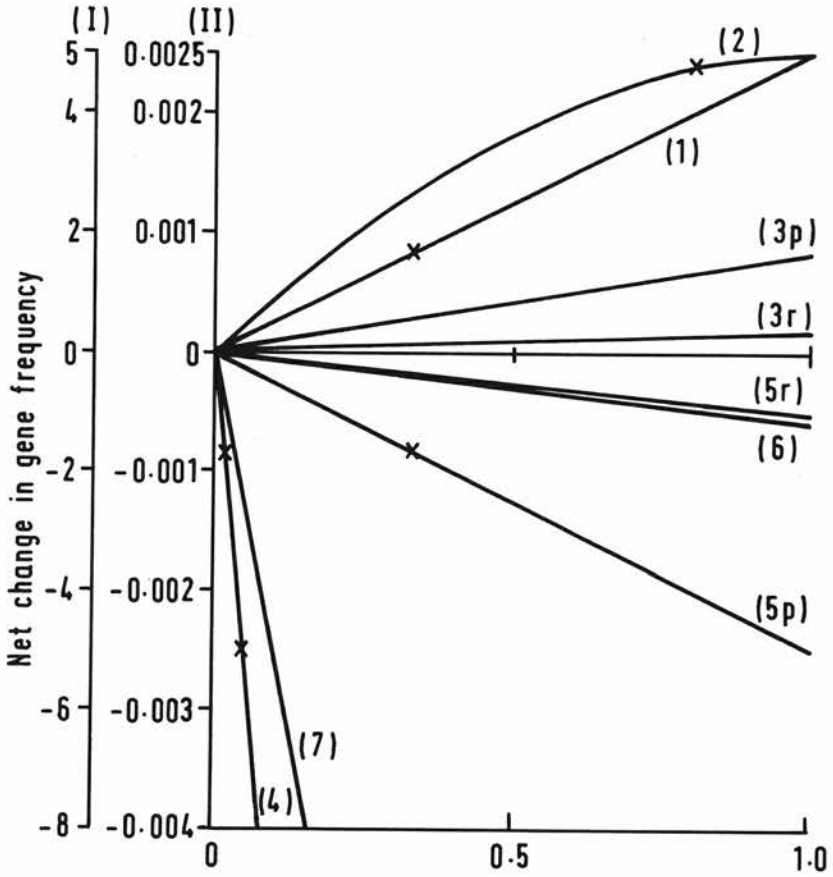

(I)
(II)
5
4
2
0
-2
-4
-6
-8
0·0025
0·002
0·001
0
-0·001
-0·002
-0·003
-0·004
Net change in gene frequency
0
0·5
1·0
(1)
(2)
(3p)
(3r)
(5r)
(6)
(5p)
(7)
(4)

Table 5.2 the change in gene frequency as a result of the introduction of improved treatments is $q^2 s'_{aa}$. The effect of increasing the fitness to 0.33 would be to produce a net increase in gene frequency of $(0.05)^2$ (0.33) = 0.0008. The percentage net change in gene frequency is $100qs'_{aa}$ = 1.65.

Family limitation by heterozygotes, heterozygous couples or sibs of affected individuals would produce a decrease in both the disease incidence and the gene frequency. It can be calculated that with the above increase in fitness of affected individuals there would be no resultant increase in gene frequency if there was a voluntary decrease in fertility of all carriers by 1.7 percent or of heterozygous couples by 25 percent. Either of these practices could therefore counterbalance the effect of an increase in the fitness of affected individuals.

Selective abortion of affected fetuses would have no effect on gene frequency unless there was reproductive compensation. However even in this case there would only be a small increase in frequency. The selection of a homozygous normal mate by carriers would produce a comparatively larger increase in gene frequency. Suppose 80 percent of carriers were to select a homozygous normal mate. The increase in gene frequency is given by $q^2 s_{aa} w_{Aa} c_i (2-w_{Aa} c_i)$ = $(0.05)^2$ (0.8) (1.2) = 0.0024 (for s_{aa} = 0). A five percent reduction in the fertility of all carriers could however counterbalance this increase. The change in gene frequency for such a reduction in fertility is given by $-q\, w_{Aa} c_i f'_{Aa}$ = -(0.05)(0.05) = -0.0025.

It seems therefore that in theory at least current forces could

reduce the incidence of sickle cell anaemia at least in the first generation even with an increase in the fitness of affected individuals. Mate selection or selective abortion with reproductive compensation, by resulting in the birth of additional heterozygous offspring, would give a potential for an increase in incidence in future generations. This increase could however be counterbalanced if only a small proportion of carriers were to reduce their family size. The size of the changes would depend on the porportions of couples adopting the various practices. With the introduction of better methods for the treatment of affected individuals heterozygous carriers might be less likely to reduce family size or to practise selective abortion and there might be a gradual increase in the incidence of the disease.

2. Porphyria variegata

Another disease with a high incidence in certain populations and with an autosomal dominant mode of inheritance is porphyria variegata. The disease has a prevalence of about 25 in 10,000 in the White population of South Africa (W.H.O. 1968) and this can be taken to be the approximate incidence of the condition if affected individuals have fitness close to unity. The corresponding gene frequency is 0.00125.

The gene is thought to have reached a high frequency because of the high fertility and low mortality of a very small number of Dutch and French settlers who went to South Africa 300 years ago. By chance one of the early settlers carried the gene for porphyria variegata. It is only in the last 50 years since the introduction of barbiturate and sulphonamide drugs that the disease has been potentially fatal.

Administration of these drugs to carriers of the gene can result in paralysis and even death. In many carriers of the gene the symptoms of the disease are so mild as not to come to the physicians attention. Because of the danger of these drugs to carriers of the gene it has been proposed that in areas like South Africa where there is a high prevalence of porphyria all the population at risk should be screened. Screening methods are very simple involving tests on urine and faeces and could result in tracing 99 percent of those who have inherited the abnormal gene, many of whom may be asymptomatic (W.H.O. 1968).

If this procedure was to be adopted individuals carrying the gene could be counselled and the genetics of the condition explained to them. Changes in the incidence of the disease and in the gene frequency which might arise as a result of family limitation or any other of the practices discussed previously can be calculated using the formulae in Table 5.3. The results obtained, taking the fitness of affected individuals to be initially unity, are plotted in Figures 7.3 and 7.4 with the base lines corresponding to an incidence of 25 in 10,000. In order to obtain the actual new incidence any changes, due to factors not considered, must be added on to those discussed below.

(i) Disease incidence

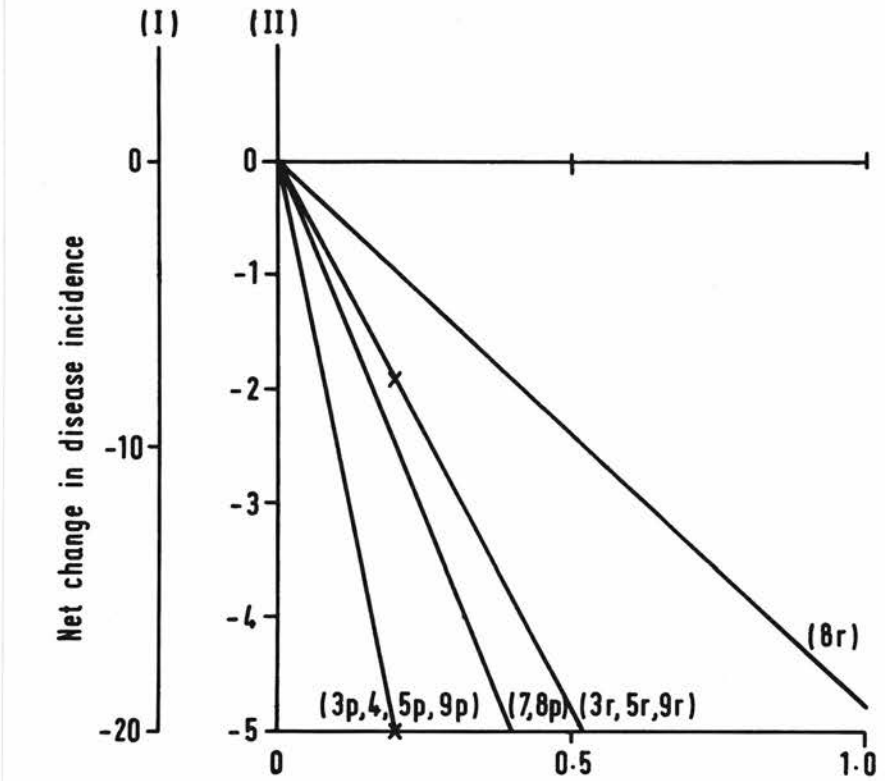
Suppose carriers of the gene were detected before they had any children and they decided to limit their family size so that there was an overall reduction in the fertility of all carriers of 20 percent. From formula B(4) in Table 5.3 the net change in incidence of carriers born would be $-2q\, w_{A-} c_i f'_{A-} (1-s_{A-}) = -2\ (0.00125)(0.2) = -5 \times 10^{-4}$. The percentage change in incidence would be $-100 w_{A-} c_i f'_{A-} (1-s_{A-}) = -20$.

Figure 7.3 Possible net changes in the incidence of porphyria variegata brought about by various practices, (I) as a percentage of the initial incidences, (II) actual change (x10,000), (relative to current practices).

Abscissa:-

Proportionate reduction in fertility (4, 5)

Proportion adopting practice (3, 7, 8, 9)


(I)
(II)
0
-10
-20
0
-1
-2
-3
-4
-5
Net change in disease incidence
(8r)
(3p,4, 5p, 9p)
(7,8p)
(3r, 5r,9r)
0
0·5
1·0

Similarly for any percentage reduction in the fertility of all carriers there would be an equal percentage reduction in incidence of carriers born. There would be the same percentage reduction in incidence if this proportion of carriers practised selective abortion of all carrier fetuses. However antenatal diagnosis is not yet possible for this condition. If carriers of the gene were only detected through an affected child the change in disease incidence would be $-2q\, w_{A-} c_i f'_{A-} P_r (1-s_{A-})$. Taking $P_r = 0.38$ as in section (6), a 20 percent reduction in the fertility of all carriers after they have had an affected child would produce a net change in disease incidence of approximately $-2(0.00125)(0.2)(0.38) = -1.9 \times 10^{-4}$. The percentage decrease in incidence would be $100 w_{A-} c_i f'_{A-} P_r (1-s_{A-}) = 100(0.2)(0.38) = 7.6$. Changes in disease incidence which would result from AI are also shown in Figure 7.3 and inspection of the formulae in Table 5.3 shows that these changes would be half of those occuring when there was family limitation by a proportion of all carriers. However AI is an even more remote possibility than selective abortion.

(ii) Gene frequency

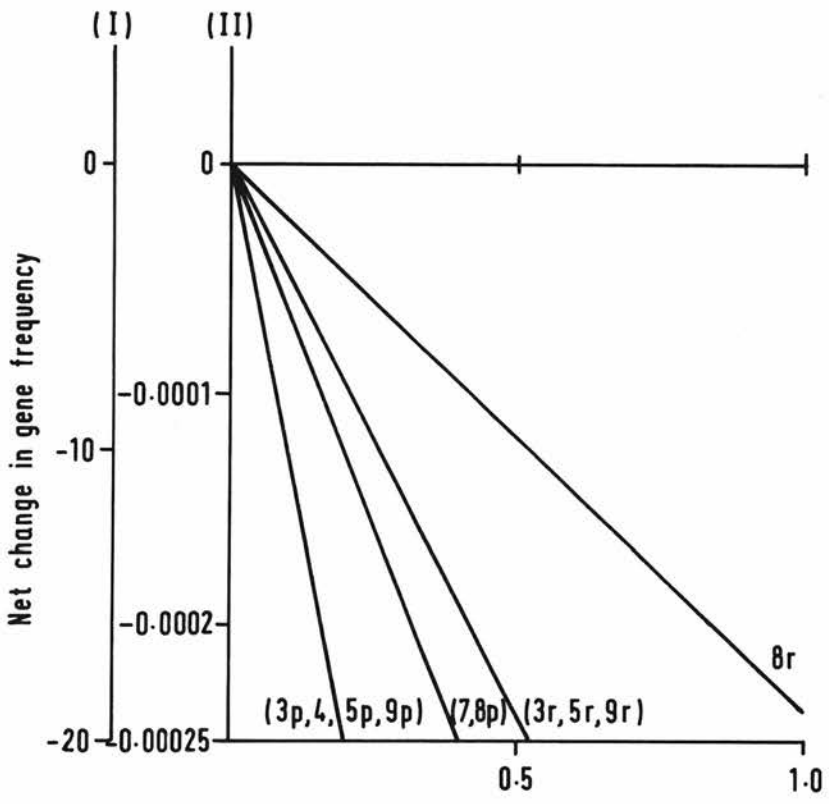
For porphyria variegata all the factors discussed above would reduce the gene frequency as well as the disease incidence. The changes in gene frequency can be calculated by substituting in the formulae in Table 5.3. Since s_{A-} is equal to zero for this disease the percentage changes in gene frequency are the same as those in disease incidence. Therefore if individuals with the deleterious gene were to limit their family size or if selective abortion or AI were possible there would be a decrease in incidence of the disease

Figure 7.4 Possible net changes in the frequency of the porphyria variegata gene brought about by various practices, (I) as a percentage of the initial frequency, (II) actual change, (relative to current practices).

Abscissa:-

Proportionate reduction in fertility (4, 5)

Proportion adopting practice (3, 7, 8, 9)


(I)
(II)
0
0
-0·0001
-10
-0·0002
-20
-0·00025
Net change in gene frequency
8r
(3p,4,5p,9p)
(7,8p)
(3r,5r,9r)
0·5
1·0

which could be maintained for more than one generation.

The changes in disease incidence and gene frequency calculated above would only occur if carriers of the gene adopted the practices. They would be more likely to co-operate in a preventitive scheme if they found the disease a handicap to themselves. If carriers did adopt these practices to any great extent the incidence of the condition might be reduced quite considerably.

3. Haemophilia A

As an example of a well known sex-linked recessive disorder consider haemophilia A. This has an incidence of about 1 in 10,000 in England (Stevenson and Kerr, 1967). In the past, few affected males reproduced, but the last few years have seen the development of improved methods of treatment so that they are enabled to lead an increasingly more normal life. Improved methods for the detection of carrier females have also been developed, one test being able to identify 90 percent of carriers (Zimmerman et al 1971).

The formulae derived above can be used to calculate possible changes in the incidence of the disease and in the gene frequency. The changes, calculated assuming the disease is initially lethal, are plotted in Figures 7.5 and 7.6. The baselines are lines corresponding to the present incidence of 1 in 10,000 and gene frequency 0.0001.

(i) Disease incidence

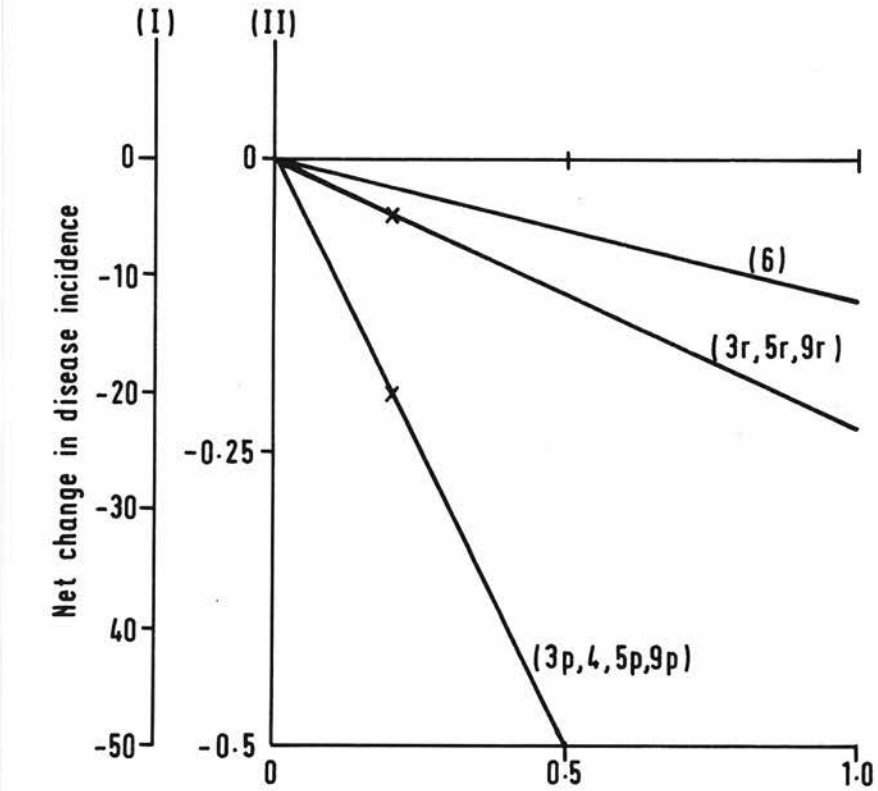
Possible changes in disease incidence can be calculated from the formulae in Table 5.5. Suppose that as a result of prospective

Figure 7.5 Possible net changes in the incidence of haemophilia brought about by various practices, (I) as a percentage of the initial, (II) actual change (x10,000), (relative to current practices).

Abscissa:-

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 9)


(I)
(II)
0
-10
-20
-30
40
-50
0
-0·25
-0·5
0
0·5
1·0
Net change in disease incidence
(6)
(3r, 5r, 9r)
(3p, 4, 5p, 9p)

ascertainment of carrier females there was a 20 percent voluntary reduction in the fertility of carriers. The change in disease incidence would be $-qw_{Aa}c_i f'_{Aa} = -(0.0001)(0.2) = -0.2 \times 10^{-4}$. The percentage change in disease incidence would be $-100w_{Aa}c_i f'_{Aa} = -100\ (0.2) = -20$. Selective abortion of all male, affected male, or affected male and carrier female fetuses by 20 percent of carrier females would produce the same decrease in incidence of haemophilia. At present only selective abortion of all male fetuses is possible but in the future it may become possible to detect affected males and carrier females in utero.

If carrier females were only detected after the birth of an affected son and there was subsequent family limitation or selective abortion smaller decreases in incidence would occur. The changes would be P_r times those for prospective detection. Taking $P_r = 0.23$ as in section (6) the change in disease incidence if there is a 20 percent reduction in the fertility of carriers after they have had an affected child is $-(0.23)(0.2) \times 10^{-4} = -0.046 \times 10^{-4}$.

(ii) Gene frequency

Possible gene frequency changes are plotted in Figure 7.6. In the past affected males rarely reproduced but now as a result of treatments their fitness is estimated to be 0.6 to 0.9 (Cavalli-Sforza and Bodmer, 1971). The net proportionate increase in gene frequency (see page 54) can be calculated from formula A(1) in Table 5.5. Suppose the fitness is increased to 0.7. The net proportionate change in incidence is $3\ s'_a\ /\ (3-s_a)(3-s_a+s'_a) = 3\ (0.7)/2(2.7) = 0.39$.

There would also be an increase in the frequency of the deleterious gene with selective abortion of all or affected males and reproductive

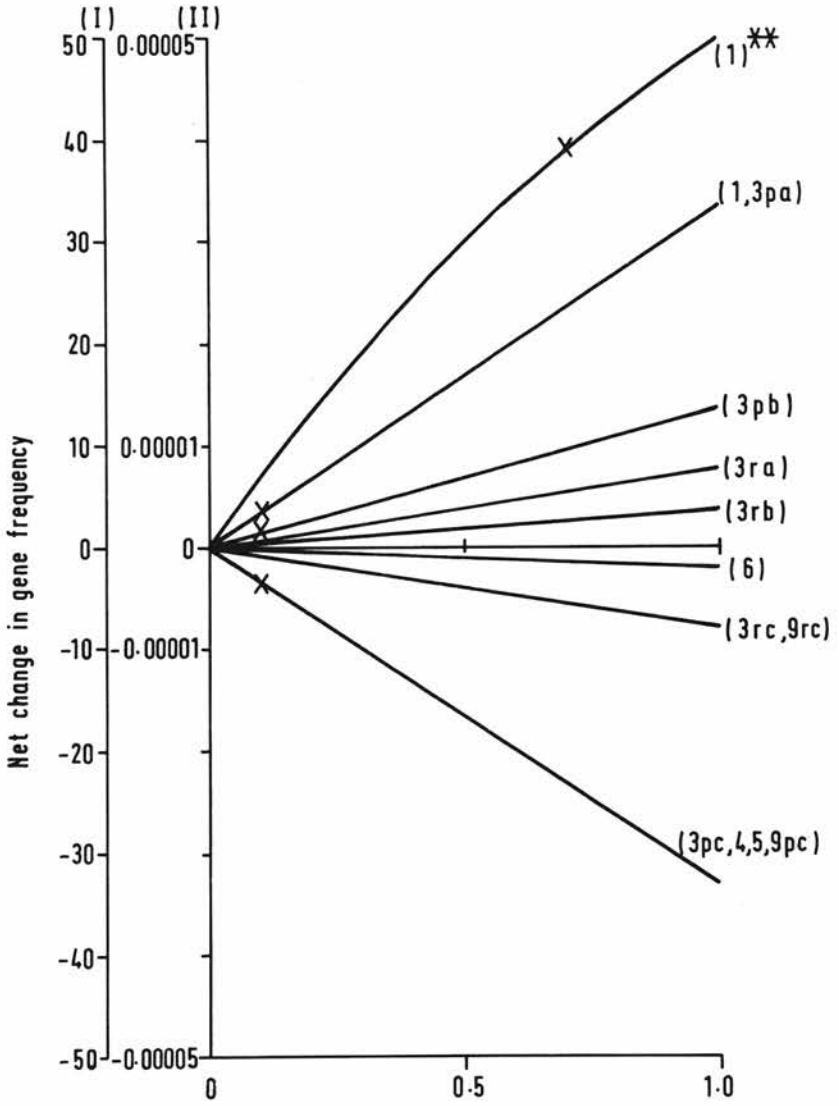
Figure 7.6 Possible net changes in the frequency of the haemophilia gene brought about by various practices, (I) as a percent of the initial frequency (II) actual changes, (relative to current practices).

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (3, 9)


(I)
(II)
50
40
30
20
10
0
-10
-20
-30
-40
-50
0·00005
0·00001
0
-0·00001
-0·00005
Net change in gene frequency
0
0·5
1·0
(1)**
(1,3pa)
(3pb)
(3ra)
(3rb)
(6)
(3rc,9rc)
(3pc,4,5,9pc)

compensation. Suppose 10 percent of carrier females were to selectively abort all male fetuses. The increase in gene frequency is given by formula A(3a) in Table 5.3. The increase is $\frac{1}{3}q\, w_m c_m s_a = (0.33)(0.0001)(0.1) = 0.000003$ for prospective detection. If affected males only, were selectively aborted the increase in gene frequency would be $\frac{1}{3}q\, w_m c_m (s_a - \frac{2}{3}) = (0.33)(0.0001)(0.1)(0.33) = 0.000001$ These increases in gene frequency would only occur if there was reproductive compensation. In the absence of reproductive compensation there would be no change in gene frequency.

There would also be a decrease in gene frequency if carrier females were to voluntarily reduce their family size. Suppose there was a decrease in fertility of carrier females of 10 percent. From formula B(4) in Table 5.5 the decrease in frequency would be $\frac{1}{3}q\, w_{Aa} c_i f'_{Aa} (2-s_a) = \frac{1}{3}(0.0001)(0.1) = 0.000003$.

It seems therefore that current forces could reduce the incidence of haemophilia in the first generation but unless they were continued into subsequent generations the frequency of the gene and hence the disease incidence, might rise. For an increase in the fitness of affected individuals to 0.7 the increase in gene frequency could only be offset by a voluntary reduction of 40 percent in the fertility of carrier females. Similarly selective abortion of all or affected male fetuses with reproductive compensation would produce a relatively large increase in gene frequency. However it is likely that if affected males had a better prognosis fewer carrier females would want to go through the trauma of intrauterine diagnosis.

(8) THE EXTENT OF THE CHANGES IN PRACTICE

In section (6) the possible changes in disease incidence and gene frequency were discussed. They were shown to be dependent both on the particular practice and on the mode of inheritance of the disease. In order to examine to what extent such changes might actually occur it is necessary to consider three other factors. These are:-

1. The feasibility of a practice i.e. the extent to which the practice is likely to be possible.
2. The proportion of individuals, for whom a particular practice is relevant, who are actually ascertained.
3. The proportion of ascertained individuals who adopt a particular practice.

The last of these was discussed in section (3), the other two will be discussed in this section.

1. Feasibility of a practice

The feasibility of any practice is dependent upon advances in medical research. All the practices considered involve one or more of the following:

a) The detection and treatment of affected individuals

b) The detection of carriers of the deleterious gene

c) The detection of the sex and/or genotype of the fetus.

a) Detection and treatment of affected individuals

If affected individuals are ascertained early enough in the progression of the disease then it is possible in at least some cases to partially cure the condition. For example in some inborn errors

of metabolism symptoms are already present in early infancy and if treatment is to achieve the maximum benefit it must be started as soon after birth as possible. Unfortunately the diagnosis is often delayed and various screening tests are therefore being developed which can be applied to all newborn infants. For example in galactosaemia and phenylketonuria serious brain damage can be prevented by early diagnosis and the placing of the affected child on a special diet.

The method of treatment used depends on the particular nature of the disease. Dietary treatment is the most common. Other possible treatments many of which are only in the experimental stage are enzyme injection, organ transplantation and attempts to modify the excretion of metabolites. So far all genetically determined diseases for which therapy is available are those in which a primary enzyme deficiency has been noted. These are all inherited by autosomal recessive or X-linked recessive mechanisms and therapy for autosomal dominant diseases is not yet available. Raine (1972) lists 181 metabolic diseases of unifactorial inheritance and classifies possible treatments as i) of established value, ii) proposed with promising preliminary results and iii) purely experimental. In 34 of the conditions (32 AR, 2 XR), the treatment is regarded as established, in 8 (all AR), as proposed and in 42 (36 AR, 6 XR) as experimental.

b) Detection of carriers of the deleterious gene

Although most recessively inherited inborn errors of metabolism are quite rare the frequency of heterozygotes is substantially higher. In some recessive diseases where the primary protein lesion is known qualitative and quantitative measurements of enzyme level in vivo or

in vitro by means of tissue culture can be used to distinguish heterozygotes. When the primary protein lesion is unknown heterozygote detection is more difficult and sometimes only successful if a metabolite is found which will serve as a marker. Of the 181 metabolic diseases listed by Raine (1972) there are 26 conditions (24 AR, 2 XR), where the heterozygote may be detected by enzyme assay and 16 (12 AR, 4 XR), where either loading tests to stress the metabolic pathway under consideration or other studies are required. It seems probable that with the identification of the primary protein lesion in more conditions and improvements in methods of enzyme assay and tissue culture, heterozygote detection should be possible for many more diseases.

c) Detection of sex and/or genotype of the fetus

For some diseases it is possible to identify an affected fetus in utero by examination of the amniotic fluid composition, staining characteristics of the cells in the fluid, or the specific enzyme activity of the cells before or after culture. If the disease can be recognised early enough it may be possible to offer selective abortion. Even if the diagnosis is not possible until too late in pregnancy to offer an abortion it may still be useful in that treatment can be initiated at the earliest possible stage. In X-linked disorders the ascertainment of fetal sex is often a substitute for prenatal detection. This may be done by sex chromatin counts, karyotype analysis, or searching for fluorescent Y chromosomes.

At present there are few diseases where an affected fetus can be detected in utero but the potential for antenatal diagnosis is considerable. In principle any Mendelian disorder in which the

biochemical lesion is known or which is associated with a distinct marker substance should be detectable in utero provided the genetic defect is expressed at an early stage. Brock (1972) lists more than 130 diseases in which the primary enzyme or protein defect has been identified with reasonable certainty. These diseases are those in which future prospects for antenatal diagnosis are brightest. All of them are recessively inherited apart from a few haemoglobinopathies. Milunsky et al (1970) list 44 inborn errors of metabolism where they believe prenatal diagnosis to be within the scope of current investigations. Raine (1972) lists 9 conditions (8 AR, 1 XR), where antenatal diagnosis has been successful in some cases and a further 14 conditions (13 AR, 1 XR), in which the deficient enzyme has been shown to be present in normal amniotic cells. If the fetus was affected therefore the enzyme deficiency might be demonstrable.

There are a large number of genetic diseases where there is currently little prospect of antenatal diagnosis. This group includes disorders of obscure origin such as Duchenne muscular dystrophy and Huntingtons chorea and those of known origin such as von Gierkes disease, phenylketonuria and beta-thalassaemia where the defect is not expressed in known tissue cells. In certain diseases where the basic biochemical lesion is unknown antenatal diagnosis may be possible if the locus of the gene which causes the disease is linked to another, the genotype at which can be detected antenatally, e.g. the locus for myotonic dystrophy is closely linked to that determining the secretor status.

Not only can affected individuals be detected in utero but in some X-linked conditions e.g. G.6.P.D. deficiency, ~~X-linked chronic~~

granulomatous disease, Lesch-Nyhan syndrome, Fabry's disease and Hunter's syndrome prenatal detection of female carriers is possible by tissue culture of fibroblasts.

Fetuses manifesting certain common congenital malformations such as anencephaly and spina-bifida, or rare unifactorial Mendelian diseases associated with a well defined morphological abnormality, can be identified by fetoscopy. In certain congenital abnormalities biochemical changes in amniotic fluid may be demonstrable and possibly even diagnostic, as in the case of alpha-feto-protein in anencephaly and spina-bifida (Brock and Sutcliffe, 1972).

Summary

From the above discussion it can be seen that although the practices are at present only possible for a limited number of diseases it is likely that they will be available for considerably more diseases in the near future. Prospects for the extension of the practices to other diseases seem most favourable for recessive diseases. Once a basic biochemical lesion has been identified this opens up the possibility for the development of therapy and also for antenatal diagnosis and heterozygote detection. There are likely therefore to be some diseases for which both eugenic and dysgenic practices are possible and others for which none are possible rather than some where only dysgenic practices are possible. This would reduce the likelihood of any increase in disease incidence or gene frequency.

For autosomal dominant diseases however the development of therapy for affected individuals seems a more remote possibility than for recessive diseases. The same is true for the detection of affected individuals in utero unless the fetus has a well defined morphological

abnormality or the probable genotype of the fetus can be determined from the genotype at a linked locus.

2. The proportion of individuals ascertained

In an attempt to obtain an estimate of the proportion of individuals ascertained by current medical practices, a study was made of families attending genetic clinics in Edinburgh and Manchester between 1965 and 1972. Data on families seen up to 1970 was published earlier (Smith et al 1971). As mentioned in the earlier paper the kinds and frequencies of the diseases studied reflect the work and interests of the Human Genetics department of Edinburgh University so that this is a study of ascertained families rather than a population study. However despite this limitation some interesting findings emerge which are probably relevant to genetic disease in general.

About 53 percent of the families were referred specifically for genetic counselling, the majority of the others being referred for diagnosis or research (Figure 8.1). The proportion referred by consultant was 67 percent, 22 percent were referred by general practitioner and a few by disease groups or through other family members. A tabulation by mode of inheritance of the numbers at risk and the number of preventible* cases is given in Table 8.1. In 146 of these families the disease was judged to be not serious or not genetic and no further persons in these families were considered to be at risk.

Often only one individual (the first contact) in these families was actually seen and counselled if this was applicable. In order to

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*Affected children born since 1960 to parents who were at high risk a priori.

Figure 8.1 Reason for referral and mode of referral in 855 families ascertained.

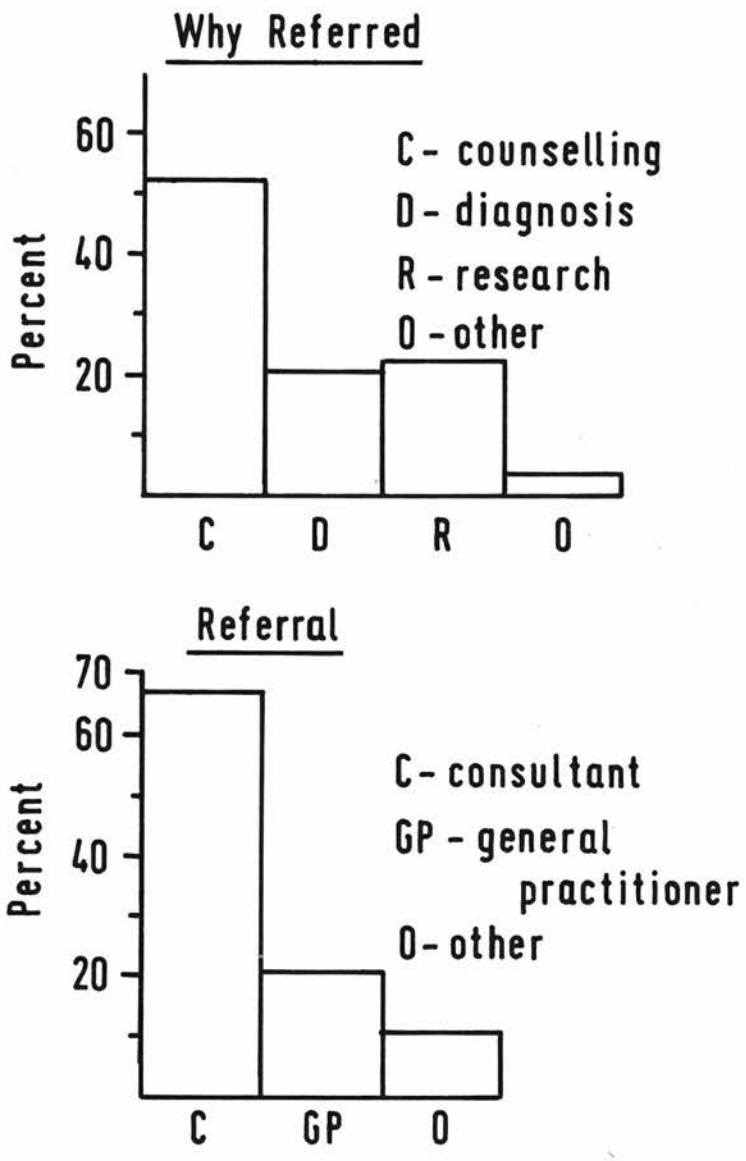

Why Referred
60
40
20
Percent
C - counselling
D - diagnosis
R - research
O - other
C
D
R
O
Referral
70
60
40
20
Percent
C - consultant
GP - general practitioner
O - other
C
GP
O

TABLE 8.1

Mode of inheritance, numbers at risk and number of preventable cases in 855 families ascertained.

	Serious Genetic Conditions					
	Mode of Inheritance					Others*
	Autosomal Dominant	Autosomal Recessive	X-linked Recessive†	Multifactorial	Chromosomal	
Families						
Number	191	172	141	159	46	146
Number with someone at risk‡	165	97	114	34	4	0
Persons						
Number at risk						
Only of becoming affected	63	6	16	12	0	0
Both of becoming affected and of having affected children**	322	0	19	5	0	0
Only of having affected children**††	242	74	327	33	4	0
Births since 1960						
at risk a priori						
Number of children affected	28	24	26	3	0	0

* Not serious, not resolved, not genetic

† 127 families with muscular dystrophy

‡ Risk 10% or higher

** Persons under age 40

†† Includes carrier daughters in X-linked disorders

obtain information about individuals currently referred to the genetic clinic, an analysis of data on first contacts was first carried out. The same calculations were then carried out using data on all individuals in the families who were judged to be at high risk ($\geq$10 percent) of becoming affected or of having an affected child. A comparison of the results of these two sets of calculations should indicate where there might be scope for ascertaining more individuals at risk in the future.

a) First Contacts

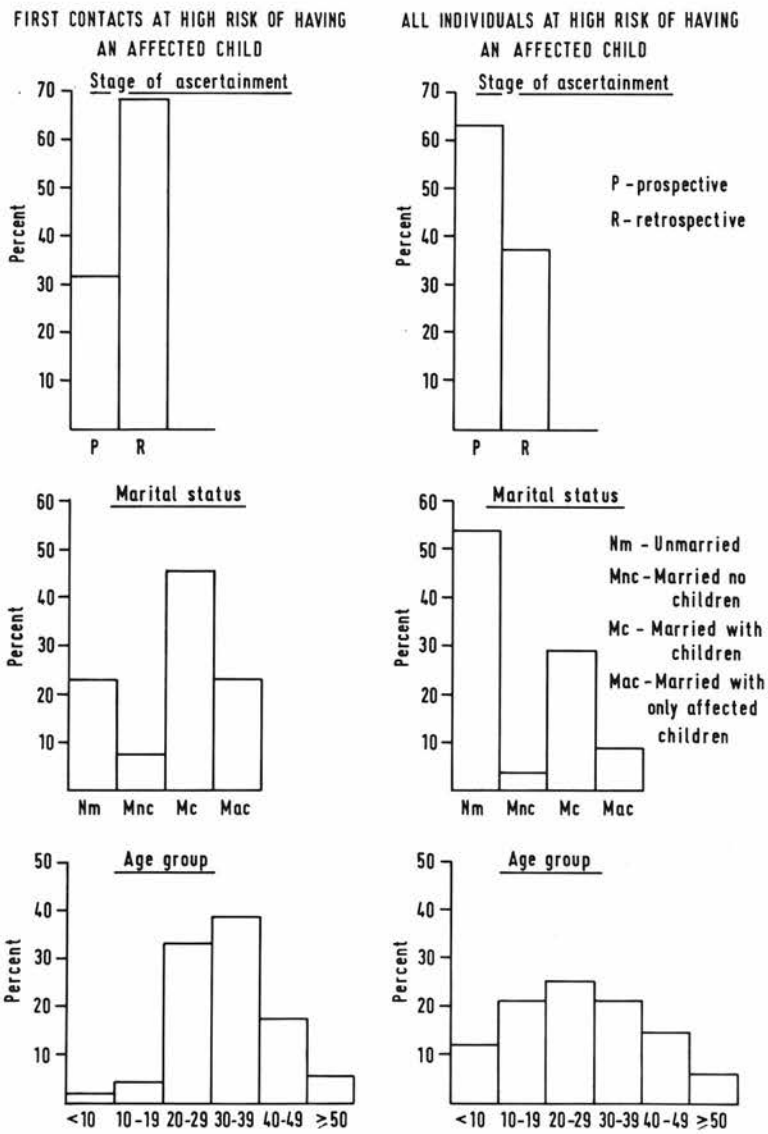
i) Individuals at high risk of becoming affected

Amongst first contacts only about one percent were at high risk of becoming affected. These were almost all in families with AD diseases but even in these families only five percent of first contacts were at risk. The great majority of first contacts were either affected (usually individuals referred for diagnosis or research) or not at risk (usually parents referred for counselling after the birth of an affected child).

ii) Individuals at high risk of having an affected child

A much greater proportion of first contacts were at high risk of having an affected child. The proportion was about 33 percent but of these two thirds were referred only after the birth of a child who was affected or at high risk of becoming affected in the future (Figure 8.2). This was reflected in the fact that 70 percent were married with children. Approximately 33 percent were aged 20-30 and 40 percent were aged 30-40 and this suggests that many may have completed their family.

Figure 8.2 Stage of ascertainment, marital status and age group of first contacts and of all individuals at high risk of having an affected child.


FIRST CONTACTS AT HIGH RISK OF HAVING AN AFFECTED CHILD
Stage of ascertainment
Percent
70
60
50
40
30
20
10
P
R
Marital status
Nm
Mnc
Mc
Mac
Age group
<10
10-19
20-29
30-39
40-49
≥50
ALL INDIVIDUALS AT HIGH RISK OF HAVING AN AFFECTED CHILD
P - prospective
R - retrospective
Nm - Unmarried
Mnc - Married no children
Mc - Married with children
Mac - Married with only affected children

b) All individuals in the families

i) Individuals at high risk of becoming affected

In addition to the first contacts there were 433 other individuals in these families who were at high risk of becoming affected. These were mainly in families with AD diseases where there was an average of two such persons per family.

ii) Individuals at high risk of having an affected child

There were 927 individuals in these families, other than first contacts, estimated to be at high risk of having an affected child. There was an average of about 2.5 such individuals in families with AD and XR diseases but less than 0.2 in families with AR and MF diseases. Of all individuals at high risk of having an affected child only about 37 percent had already given birth to a child who was affected or at high risk of becoming affected and about 54 percent were unmarried (Figure 8.2).

Comparison of results on first contacts and all individuals at high risk

It seems that with current methods of ascertainment the practices discussed would have little effect on disease incidence and gene frequency. At present few individuals at risk of developing genetic diseases are detected most individuals being referred to the clinic only after the onset of definite symptoms of the disease when any therapy might be less effective. Most individuals at high risk of having an affected child are only referred after the birth of one or more such children. This would reduce the effect on the gene pool of their adopting one of the practices subsequent to counselling. Many may have already completed their family and would not adopt any of the practices for this reason.

If an effort was made to contact other family members there could be greater changes in disease incidence and gene frequency at least in AD and XR diseases. In families with these diseases first contacts have many relatives at high risk of becoming affected or of having affected children. Relatives at risk of becoming affected are mainly in families with late onset AD diseases where the introduction of any therapy, while being of advantage to the individual himself would only have an effect on the gene pool if onset was before the individual had had offspring. Of individuals at high risk of having an affected child 63 percent had not yet had an affected child and 54 percent were unmarried. If such individuals were counselled and they subsequently decided to reduce their family size there could be a larger reduction in disease incidence. Any affected children they did have could be diagnosed early and offered therapy if it was available.

In families with AR and MF diseases there were comparatively few individuals at risk. In most of these families both mother and the affected child (if alive) were seen at the clinic and there were no other family members at high risk of becoming affected or of having an affected child. Therefore in these families contacting relatives would reveal few individuals at risk who might adopt one of the practices. Screening individuals in families with AR diseases could reveal heterozygotes who might subsequently reduce their family size but the effect on the gene pool would be small as these would be a small proportion of all heterozygotes. To detect, prospectively, individuals at high risk of having children with AR diseases, screening would have to be extended beyond the families of affected individuals.

In addition to the effect of detection of more couples at risk prospectively there might also be greater changes in the incidence of

diseases of all modes of inheritance if more couples were detected before they had had more than one affected child. For example there were 95 couples who had had at least one child affected with an AR disease. Of these children 24 had been born since 1960 to couples who were at high risk a priori. These births might have been prevented if the couples had been informed of their risks as soon as the first affected child was diagnosed.

These results indicate that with current methods of ascertainment the effect of any of the practices would be minimal. Greater changes could occur if more individuals were detected after the birth of a first affected child rather than later when their family might be complete. In AD and XR diseases there is also considerable scope for detecting individuals at risk prospectively by contacting relatives of individuals referred.

In the Human Genetics department at Edinburgh University a Register for the Ascertainment and Prevention of Inherited Disease (RAPID) has been developed. The RAPID system is being used for the follow-up of individuals who have been counselled and also for contacting and counselling others at risk in the family. In addition, in an effort to contact even more individuals at risk, families have been ascertained through hospital and health department records and disablement registers. If this was extended to other areas and individuals ascertained adopted the practices much greater changes in disease incidence and gene frequency might occur.

(9) EQUILIBRIUM FREQUENCIES OF GENETIC DISEASES

In the preceeding sections only single generation changes in disease incidence and gene frequency were considered. This was because these will be more important in practice than long term changes. It is however relatively easy to calculate equilibrium frequencies of these diseases for any of the practices discussed earlier. The equilibrium frequencies, resulting from the adoption of one or more of the practices, can be calculated in terms of the reproductive fitnesses of individuals with the deleterious gene. The derivation of formulae for calculating equilibrium frequencies of X-linked recessive diseases was described in an earlier study (Holloway and Smith (1973)). In this section formulae for the equilibrium frequencies of diseases with an autosomal recessive, autosomal dominant and X-linked recessive mode of inheritance will be derived. The formulae will then be used to derive possible equilibrium frequencies for sickle-cell anaemia (AR), porphyria variegata (AD) and haemophilia (XR).

FORMULAE WHEN FITNESS VALUES ARE KNOWN

1) AR diseases

Consider three genotypes AA, Aa and aa as before with initial frequencies p^2, $2pq$ and q^2 respectively. Let the frequencies of Aa and aa in any generation be denoted by C_R and A_R. It is assumed that affected individuals have fitness of zero. This has been approximately true for most AR diseases at least until recently and as shown earlier the frequency of affected individuals is much more influenced by the reproductive practices of heterozygotes than those of affected individuals. The three possible mating types together

with their frequencies and fitnesses and the genotype distributions of the offspring are given below.

Mating type	Frequency	Fitness	Proportions of offspring AA	Aa	aa
AA x AA	$(1-C_R)^2$	1	1	0	0
Aa x AA	$2C_R(1-C_R)$	F_1	$\frac{1}{2}$	$\frac{1}{2}$	0
Aa x Aa	C_R^2	F_2	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$

F_1 and F_2 are the relative fitnesses of (Aa x AA) and (Aa x Aa) couples respectively compared to (AA x AA) couples. For a completely recessive gene with no heterozygote advantage they are both equal to one unless any of the above practices (such as family limitation) is adopted.

Affected individuals are either the offspring of (Aa x Aa) couples or result from a mutation in a gamete which subsequently unites with one carrying the a allele. The frequency of the latter event is approximately equal to the product of the frequency of carriers and the mutation rate μ. (Affected individuals could also result from mutations in both gametes of the uniting pair but this event is so rare that it can be ignored). Therefore at equilibrium

$$A_R = \frac{1}{4}F_2 C_R^2 + \mu C_R \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 9.1$$

Carriers arise from a mutation in either gamete of the uniting pair or are the offspring of carriers, one half of whose offspring are also carriers. Therefore at equilibrium $C_R = 2\mu + \frac{1}{2}F_1 \cdot 2C_R(1-C_R) + \frac{1}{2}F_2 C_R^2$

$$C_R = 2\mu + F_1 (C_R - C_R^2) + \frac{1}{2}F_2 C_R^2 \quad \ldots\ldots\ldots \quad 9.2$$

The equilibrium frequencies of affected and carrier individuals

can thus be found in terms of the mutation rate by substituting appropriate values of F_1 and F_2 into equations 9.1 and 9.2. For example consider the situation where none of the (Aa x Aa) couples has any children so that $F_2 = 0$ and (Aa x AA) couples have a normal family size so that $F_1 = 1$.

Then from equation 9.2 $C_R^2 = 2\mu$ $C_R = \sqrt{2\mu}$

Substituting in equation 9.1 gives $A_R = \mu \sqrt{2\mu}$

2) AD diseases

Consider two genotypes Aa and aa with initial frequencies 2pq and p^2. Individuals of genotype AA are ignored as previously. Let the frequency of Aa individuals in any generation be A_D. The mating types together with their frequencies and fitnesses and the genotype distributions of the offspring are given below. It is assumed that Aa individuals are rare and marriages involving two affected partners are ignored.

Mating type	Frequency	Fitness	Proportions of offspring		
			AA	Aa	aa
Aa x aa	$2A_D(1-A_D)$	F_3	0	$\frac{1}{2}$	$\frac{1}{2}$
aa x aa	$(1-A_D)^2$	1	0	0	1

Affected individuals arise from a new mutation in either gamete or are the offspring of affected individuals, one half of whom are also affected.

Therefore at equilibrium $A_D = 2\mu + \frac{1}{2} \cdot 2A_D (1-A_D) F_3$ which approximates to

$$A_D = 2\mu + A_D F_3 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 9.3$$

Given the value of F_3 the equilibrium frequency of affected individuals can be calculated. For example if $F_3 = 0$, $A_D = 2\mu$ and if $F_3 = 0.9$, $A_D = 20\mu$.

3) XR diseases

The genotypes are for females, AA and Aa with initial frequencies p^2 and 2pq and for males AY and aY with initial frequencies p and q. Affected females are ignored as previously. Let the frequencies of Aa and aY individuals in any generation be C_x and A_x respectively. It is assumed that affected males and carrier females are sufficiently rare to make the numbers of marriages between them negligable. Therefore the mating types are as follows:-

Mating type	Frequency	Fitness	Proportions of offspring			
			Females		Males	
			AA	Aa	AY	aY
AA x AY	$(1-C_x)(1-A_x)$	1	1	0	1	0
AA x aY	$A_x(1-C_x)$	F_4	0	1	1	0
Aa x AY	$C_x(1-A_x)$	F_5	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$

Affected males either arise from a new mutation or are the offspring of carrier females, half of whose sons are affected. Therefore at equilibrium $A_x = \mu + \frac{1}{2} F_5 C_x (1-A_x)$ which approximates to

$$A_x = \mu + \frac{1}{2} F_5 C_x \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 9.4.$$

Similarly, carrier females can arise by new mutation, from affected males (all daughters are carriers), or from carrier mothers (half their daughters are carriers). Therefore at equilibrium

$C_x = 2\mu + F_4 A_x (1-C_x) + \frac{1}{2} F_5 C_x (1-A_x)$ which approximates to

$$C_x = 2\mu + F_4 A_x + \frac{1}{2} F_5 C_x \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 9.5.$$

The equilibrium frequencies of affected males and of carrier females can be found by substituting values of F_4 and F_5 in these equations. For example if $F_4 = 0$ and $F_5 = 1$, as for a lethal condition where there is no family limitation by carrier females, then $A_x = \mu + \frac{1}{2} C_x$ and

$C_x = 2\mu + \frac{1}{2} C_x$. This gives $C_x = 4\mu$ and $A_x = 3\mu$.

CALCULATION OF THE FITNESS VALUES

From the above it can be seen that when the fitness values are known the equilibrium frequencies of affected individuals can be calculated. In practice, however, the values of F_1, F_2 etc. are not known simply but depend both on the reproductive fitness of affected individuals and on the proportions of couples adopting the various practices. If individuals at risk of having an affected child are detected prospectively and have no children their fitness is zero. If they terminate their family retrospectively i.e. after the birth of an affected child their fitness if P_r (see page 65). Any who partially restrict their family after detection have a fitness less than unity and those who go on to have a normal family size have a fitness of unity.

If there is selective abortion, AI, or partner selection by heterozygous carriers (in AR diseases), then in addition to possible changes in the net reproductive fitness there are changes in the proportions of offspring of different genotypes who are born. This must be taken into account in the calculation of the fitness values. Suppose x_{ij} is the ratio of the number of individuals of genotype ij born after the adoption of any one of the practices to the number born before the practice is adopted. Then for AR diseases:-

$$F_1 = \frac{1}{2} (x_{AA} + x_{Aa}) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 9.6$$

$$F_2 = \frac{1}{4} (x_{AA} + 2x_{Aa} + x_{aa}) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 9.7$$

For example if one half of (Aa x Aa) couples have no children the fitness of these couples (F_2) is one half. The values of x_{AA}, x_{Aa}

and x_{aa} are also one half and substituting these values in equation 9.7 gives $F_2 = \frac{1}{4}(\frac{1}{2} + 1 + \frac{1}{2}) = \frac{1}{2}$ as expected.

If (Aa x Aa) couples were to practice selective abortion of all aa fetuses without reproductive compensation then $x_{AA} = x_{Aa} = 1$ and $x_{aa} = 0$ thus $F_2 = \frac{1}{4}(1 + 2 + 0) = \frac{3}{4}$.

If there was selective abortion with full reproductive compensation so that a normal family size was produced then $F_2 = 1$. Additional AA and Aa individuals would be born in the ratio 1:2. To calculate the values of x_{AA} and x_{Aa} consider families of size 4. With no selective abortion there will be an average of 1 AA individual, 2 Aa individuals and 1 aa individual. With selective abortion and reproductive compensation there will be an average of 1.33 AA individuals, 2.67 Aa individuals and no aa individuals. Therefore

$x_{AA} = \frac{1.33}{1} = 1.33$ and $x_{Aa} = \frac{2.67}{2} = 1.33$, $x_{aa} = \frac{0}{1} = 0$

giving $F_2 = \frac{1}{4}[1.33 + 2.67 + 0] = 1$ as expected.

Similar expressions can be obtained for F_3, F_4 and F_5. For AD diseases

$$F_3 = \frac{1}{2}(x_{Aa} + x_{aa}) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 9.8$$

For XR diseases the overall fitness values are the averages of those for male and female offspring. Therefore $F_4 = \frac{1}{2}(x_{Aa} + x_{AY})$ 9.9

$F_5 = \frac{1}{2}[\frac{1}{2}(x_{AA} + x_{Aa} + x_{AY} + x_{aY})] = \frac{1}{4}(x_{AA} + x_{Aa} + x_{AY} + x_{aY})$ 9.10

GENERAL FORMULAE FOR EQUILIBRIUM FREQUENCIES

Equations 9.1 to 9.5 can now be combined with equations 9.6 to 9.10 to obtain a single set of formulae for the equilibrium frequencies of diseases of each mode of inheritance.

1) AR diseases

Let the subscript i refer to the symbols for the ith group of (AA x Aa) couples who make up a proportion P_i of all such couples. Similarly let the subscript j refer to the symbols for the jth group of (Aa x Aa) couples who make up a proportion P_j of such couples. Let z_i and z_j be the proportions of offspring born to the respective couples before detection. In particular if (Aa x Aa) couples are detected after the birth of an affected child then $z_j = (1-P_r)$.

Combining equations 9.1 and 9.7 we obtain:-

$$A_R = \mu C_R + \frac{1}{4} C_R^2 \sum_{j=1}^{\infty} P_j [z_j + (1-z_j) x_{aa_j}] \quad \ldots\ldots\ldots\ldots\ldots 9.11$$

Combining equations 9.2, 9.6 and 9.7 we obtain:-

$$C_R = 2\mu + (C_R - C_R^2) \sum_{i=1}^{\infty} P_i [z_i + (1-z_i) x_{Aa_i}]$$
$$+ \frac{1}{2} C_R^2 \sum_{j=1}^{\infty} P_j [z_j + (1-z_j) x_{Aa_j}] \quad \ldots\ldots\ldots\ldots\ldots\ldots 9.12$$

2) AD diseases

For AD diseases if we combine equations 9.3 and 9.8 we obtain

$$A_D = 2\mu + A_D \sum_{i=1}^{\infty} P_i [z_i + (1-z_i) x_{Aa_i}] \quad \ldots\ldots\ldots\ldots\ldots\ldots 9.13$$

Where the subscript i refers to the ith group of Aa individuals who make up a proportion P_i of all Aa individuals and z_i is the proportion of offspring born before detection.

3) XR diseases

Let the subscript i refer to the symbols for the ith group of carrier females who make up a proportion P_i of all such females and the subscript j refer to the symbols for affected males. The equilibrium frequencies of affected males and of carrier females can then

be found by combining equations 9.4, 9.5, 9.9 and 9.10 giving:-

$$A_x = \mu + \frac{1}{2} C_x \sum_{i=1}^{\infty} P_i \left[z_i + (1-z_i)\, x_{AY_i} \right] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 9.14$$

$$C_x = 2\mu + A_x \sum_{j=1}^{\infty} P_j \left[z_j + (1-z_j)\, x_{Aa_j} \right] + \frac{1}{2} C_x \sum_{i=1}^{\infty} P_i \left(z_i + (1-z_i)\, x_{Aa_i} \right] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 9.15$$

EQUILIBRIUM FREQUENCIES OF COMMON DISEASES

To illustrate the use of these formulae consider as examples the three diseases discussed in section (7). These are sickle cell anaemia, porphyria variegata and haemophilia with AR, AD and XR modes of inheritance respectively.

1) Sickle-cell anaemia

Equations 9.11 and 9.12 can be used to calculate possible equilibrium frequencies of this disease for various reproductive policies of heterozygous carriers, assuming that affected individuals have a fitness of zero. Suppose that couples are screened before having any children and that as a result 50 percent of (Aa x AA) couples and 50 percent of (Aa x Aa) couples are ascertained. Of the (Aa x AA) couples ascertained suppose nine tenths go on to have a normal family size and one tenth have no children and that all the couples not ascertained have normal family size. Of the (Aa x Aa) couples suppose that for an additional 30 percent those ~~are detected after~~ having an affected child are detected and that after detection, whether this is prospective or retrospective, one quarter have a normal family size, one quarter have no children, one quarter practise selective abortion of affected fetuses without reproductive compensation and the remaining quarter practise selective abortion with reproductive compensation. The 20 percent of couples still undetected are assumed to have a normal family size.

Table 9.1

Proportions of couples by stage of detection and reproductive policy as used in the example for sickle cell anaemia (see page 117).

Reproductive policy	Stage of detection		
	Undetected	Prospective	Retrospective
Aa x AA			
Normal family size	0.5	0.45	0
No offspring	0	0.05	0
Aa x Aa			
Normal family size	0.2	0.125	0.075
No offspring	0	0.125	0.075
Selective abortion without reproductive compensation	0	0.125	0.075
Selective abortion with reproductive compensation	0	0.125	0.075

This is summarised in Table 9.1. From equation 9.11

$$A_R = \mu C_R + \frac{1}{4} C_R^2 \sum_{j=1}^{\infty} P_j [z_j + (1-z_j) x_{aa_j}]$$

$$\sum_{j=1}^{\infty} P_j [z_j + (1-z_j) x_{aa_j}]$$

$$= 0.2(1) + 0.125\ (0+1) + 0.125\ (0+0) + 0.125\ (0+0) + 0.125\ (0+0)$$

$$+ 0.075\ (0.77+0.23(1)) + 0.075\ (0.77+0.23(0)) + 0.075\ (0.77+0.23(0))$$

$$+ 0.075\ (0.77+0.23(0)) = 0.573$$

$$A_R = \mu C_R + \frac{1}{4} C_R^2 \cdot 0.573$$

$$A_R = \mu C_R + 0.143 C_R^2$$

Similarly from equation 9.12 $C_R = 2\mu + 0.95\ (C_R - C_R^2) + \frac{1}{2} C_R^2\ (0.905)$

For $\mu = 10^{-5}$ this gives $C_R \doteq 40\mu$ and $A_R \doteq 270\mu^2$

Thus the equilibrium frequency of sickle cell anaemia under these purely hypothetical conditions would be $270\mu^2$.

2) Porphyria variegata

Possible equilibrium frequencies of this disease can be calculated from equation 9.13. Suppose that 80 percent of carriers of the gene are detected prospectively and of these one half have a normal family size and one half either have no children or practise selective abortion of affected fetuses. The actual proportions having no children and practising selective abortion are immaterial since which ever practice is adopted no affected offspring are born. The 20 percent of carriers remaining undetected are assumed to have a normal family size. This is summarised in Table 9.2.

From equation 9.13 $A_D = 2\mu + A_D \sum_{i=1}^{\infty} P_i [z_i + (1-z_i) x_{Aa_i}]$

Substituting in this equation gives $A_D = 2\mu + A_D [0.2 + 0.4\ (0+1)$

$$+ 0.4\ (0+1(0))]$$

$$0.4\ A_D = 2\mu \qquad A_D = 5\mu$$

Table 9.2

Proportions of affected individuals by stage of detection and reproductive policy as used in the example for porphyria variegata (see page 118).

Reproductive policy	Stage of detection		
	Undetected	Prospective	Retrospective
Normal family size	0.2	0.4	0
No offspring or selective abortion	0	0.4	0

Under these hypothetical conditions therefore the equilibrium frequency of the disease is 5μ.

3) Haemophilia

By substituting in equations 9.14 and 9.15 possible equilibrium frequencies of haemophilia can be obtained. For example consider the following hypothetical situation. Amongst affected males suppose that 30 per cent do not survive to reproduce, a further 30 per cent have no offspring and 40 per cent have a normal family size. Of carrier females suppose 20 per cent are undetected and have a normal family size and that another 20 per cent are detected prospectively and, for those having an affected child are ascertained 60 per cent ~~retrospectively.~~ After detection suppose that one quarter have a normal family size, one quarter have no children and one half practise selective abortion of all male fetuses, half of these without reproductive compensation and half with reproductive compensation so having a normal family size. This is summarised in Table 9.3.

From equation 9.14 $A_x = \mu + \frac{1}{2} C_x \sum_{i=1}^{\infty} P_i [z_i + (1-z_i) x_{AY_i}]$

$\sum_{i=1}^{\infty} P_i [z_i + (1-z_i) x_{AY_i}] = 0.2(1) + 0.05 [0+1(1)] + 0.05 [0+1(0)]$

$+ 0.05 [0+1(0)] + 0.05 [0+1(0)] + 0.15 [0.77+0.23(1)] + 0.15 [0.77+0]$

$+ 0.15 [0.77+0] + 0.15 [0.77+0]$

$= 0.2 + 0.05 + 0.15 (1+3(0.77)) = 0.7465$

Equation 9.14 therefore becomes $A_x = \mu + 0.3733 C_x$.

Similarly equation 9.15 becomes $C_x = 2\mu + 0.4 A_x + \frac{1}{2} C_x$

Solving equations 9.14 and 9.15 gives $C_x = 6.84\mu$ $A_x = 3.55\mu$ i.e. the equilibrium frequency of haemophilia under these hypothetical conditions would be about 3.55μ.

Table 9.3

Proportions of affected males and carrier females by stage of detection and reproductive policy as used in the example for haemophilia (see page 119).

Reproductive policy	Stage of detection		
	Undetected	Prospective	Retrospective
Affected males			
Not surviving	0	0.3	0
No offspring	0	0.3	0
Normal family size	0	0.4	0
Carrier females			
Normal family size	0.2	0.05	0.15
No offspring	0	0.05	0.15
Selective abortion without reproductive compensation	0	0.05	0.15
Selective abortion with reproductive compensation	0	0.05	0.15

CONCLUSIONS

The formulae derived above can be used to calculate possible equilibrium frequencies for any unifactorial genetic disease, where affected individuals are rare and have a low fitness. In order to use these formulae it is necessary to know both the proportions of individuals adopting the various practices and their reproductive fitnesses. For any practice the reproductive fitness of individuals with the deleterious gene can be calculated (see page 114). It is however difficult to obtain reliable estimates of the proportions of individuals of a particular genotype who are detected and the proportions adopting particular practices. Even if these values were known for one generation it is most unlikely that they would remain constant in successive generations. The equilibrium frequencies calculated will therefore be of theoretical interest only.

The theoretical equilibrium frequencies calculated for sickle cell anaemia, porphyria variegata and haemophilia are considerably smaller than the initial frequencies. These new frequencies are independent of the initial frequencies of the diseases and are thus applicable to any disease with the same mode of inheritance and same values of the fitness parameters. However these examples were chosen simply to illustrate the use of the formulae and in practice the proportions of individuals detected and adopting any of the practices are likely to be much smaller than in the examples. The corresponding equilibrium frequencies would therefore be closer to the initial frequencies.

(10) DISCUSSION

In this thesis an attempt has been made to measure possible changes in the incidence of genetic diseases and in the frequencies of the corresponding deleterious alleles which might arise as the result of current and future medical practices. In an effort to summarise the large number of results and the range of disease conditions to which they may apply, qualitative scores have been assigned to show the possible effects of the practices. These are given in Tables 10.1 and 10.2. The feasibility of the practices, for diseases of different modes of inheritance, have been assessed largely on the basis of the discussion in section 8.1 and the results are given in Table 10.3. The extent to which any of the practices might be used, if available, is discussed later.

Considering together the possible effects (Table 10.1) and feasibility of application (Table 10.3) indicates that the overall effect of the various practices studied is likely to be a general decrease rather than an increase, in the incidence of genetic diseases in the next generation. The only practice (improved treatment) which could cause increases in incidence could only produce a relatively small increase in incidence of XR and MF diseases and AR diseases where there is no heterozygote advantage. Larger increases could occur in AR diseases with heterozygote advantage or in AD diseases but in the latter case therapy is rarely available. Similarly considering together Tables 10.2 and 10.3 shows that for AR or AD diseases possible decreases in gene frequency are greater than possible increases for the practices available at present. In these cases therefore there is likely to be a longer term decrease in disease

TABLE 10.1

Summary of possible changes in disease incidence for diseases of early onset where affected individuals have low fitness

PRACTICE	Net proportionate change in disease incidence						
	AR	AR(HA)	AD	AD+	XR		MF
1. Improved treatment	+	++	+++	++	+		+
2. Selection of mate	---	---					
3. Selective abortion with reproductive compensation: prospective	---	--	-	-	a b c	--- --- ---	(-)(--)
3. Selective abortion with reproductive compensation: retrospective	--	--	-	--	a b c	-- -- --	-
4. Family limitation by carriers	---	---	-	-	---		(-)(--)
5. Family limitation by carriers at risk: prospective	---	---	-	-	---		(-)(--)
5. Family limitation by carriers at risk: retrospective	--	--	-	--	--		-
6. Family limitation by sibs of affected individuals	-	-	0	--	--		-
7. AI for spouses of carrier males	---	---	-	-	0		
8. AI for spouses of carrier males at risk: prospective	---	---	-	-			
8. AI for spouses of carrier males at risk: retrospective	--	--	-	-			
9. Selective abortion without reproductive compensation: prospective	---	---	-	-	a b c	--- --- ---	(-)(--)
9. Selective abortion without reproductive compensation: retrospective	--	--	-	--	a b c	-- -- --	-

(+++) (---) Maximum theoretical change ~~<10%~~ >50%

(++) (--) Maximum theoretical change 10-50%

(+) (-) Maximum theoretical change ~~>50%~~ <10%

TABLE 10.2

Summary of possible changes in gene frequency for diseases of early onset where affected individuals have low fitness

PRACTICE	Net proportionate change in gene frequency					
	AR	AR(HA)	AD	AD^+	XR	
1. Improved treatment	+	++	+++	++	++	
2. Selection of mate	+	+				
3. Selective abortion with reproductive compensation: prospective	+	+	-	+	a ++ b ++ c --	
3. Selective abortion with reproductive compensation: retrospective	+	+	-	+	a + b + c -	
4. Family limitation by carriers	---	---	-	-	--	
5. Family limitation by carriers at risk: prospective	-	--	-	-	--	
5. Family limitation by carriers at risk: retrospective	-	-	-	-	-	
6. Family limitation by sibs of affected individuals	-	-	0	-	-	
7. AI for spouses of carrier males	---	--	-	-	-	
8. AI for spouses of carrier males at risk: prospective	-	-	-	-		
8. AI for spouses of carrier males at risk: retrospective	-	-	-	-		
9. Selective abortion without reproductive compensation: prospective	-	-	-	-	a - b - c --	
9. Selective abortion without reproductive compensation: retrospective	-	-	-	-	a - b - c -	

(+++) (---) Maximum theoretical change ~~<10%~~ > 50%

(++) (--) Maximum theoretical change 10-50%

(+) (-) Maximum theoretical change ~~>50%~~ < 10%

TABLE 10.3

An assessment of the feasibility of applying the various practices at present or in the future

PRACTICE		Feasibility of practice				
		AR	AD	XR		MF
1. Improved treatment		++	+	++		++
2. Selection of mate		++				
3. Selective abortion with reproductive compensation	prospective	++	+	a b c	++ + +	+
	retrospective	+++	+	a b c	+++ ++ +	++
4. Family limitation by carriers		++	+++	++		+
5. Family limitation by carriers at risk	prospective	++	+++	++		+
	retrospective	+++	+++	+++		+++
6. Family limitation by sibs of affected individuals		+++	+++	+++		+++
7. AI for spouses of carrier males		++	+++	++		
8. AI for spouses of carrier males at risk	prospective	++	+++			
	retrospective	+++	+++			
9. Selective abortion without reproductive compensation	prospective	++	+	a b c	++ + +	+
	retrospective	+++	+	a b c	+++ ++ +	++

+++ Usually feasible

++ Sometimes feasible

+ Rarely feasible

incidence. In XR diseases however there is a possibility of a longer term increase in disease incidence as a result of improved therapy or selective abortion with reproductive compensation.

Usage of practices

The adoption of any particular practice would depend upon the individual disease and the availability of other practices. For example if effective therapy was introduced for a disease couples at risk of having an affected child might be less likely to limit their family size ~~of~~ or abort affected fetuses giving a possible increase in incidence in future generations. However treated individuals might voluntarily decide to have no offspring and some treatments might simply increase the life span of affected individuals but leave them biologically infertile. Warwick (1968) showed that the median age of death of individuals with cystic fibrosis was 8 months before treatment was available, but now, in one clinic where there is intensive prophylactic treatment, it is 21 years. However only about 2-3 percent of affected males are fertile (Taussig et al (1972)) and though women have reproduced the risk of pregnancy to maternal and fetal health may be great (Grand et al 1966).

If heterozygotes could be detected it seems likely that they would only reduce their family size if they had a high risk of having affected children. In AD and XR diseases all heterozygotes would fall into this category but in AR diseases only heterozygotes married to another heterozygote would be at risk. If heterozygotes for deleterious AR genes were detected before marriage they might prefer to avoid having affected children by selecting a marriage partner who is not also heterozygous. In the U.S.A. efforts have been made

to screen Blacks for sickle-cell trait while still at school (Culliton, 1972b) and this might result in more selection of marriage partner than if screening was not done until individuals were older when many might be already engaged or married.

Couples at risk might not be detected until they had had an affected child. The results discussed in the literature review suggest that in this case couples would be less likely to initiate a further pregnancy if their affected child was likely to live for some time or require much care and attention.

For diseases in which selective abortion is possible some couples might prefer to use it rather than reduce their family size. The results discussed in the literature review suggest an increasing acceptance of abortion particularly when a fetus can be positively identified as being affected. In Tay-Sachs disease and Pompe's disease couples at risk can be identified by screening and doctors can tell if any fetus has the disease early enough to perform an abortion. AI is another possibility but it is uncertain how many couples would use it as it has not yet been widely offered.

General considerations

The implementation of any of these practices on a large scale might introduce several new problems both practical, e.g. an increased demand for resources and ethical e.g. rights of individuals to reproduce. Some of these are discussed below.

a) Demand for resources

Any increase in the numbers of individuals using these practices would be accompanied by an increased demand for material resources and for trained personnel. For example there might be an increased

demand for special diets or drugs for affected individuals. In phenylketonuria, maple syrup urine disease and galactosaemia affected individuals require highly purified diets with specially regulated quantities of certain metabolites. Individuals with cystic fibrosis require long term administration of antibiotics and agents to liquefy viscid bronchial secretions.

If individuals were screened for carrier status or to detect a disease in its early stages additional laboratory facilities would be required for testing samples. There would also be a need for personnel to counsel individuals ascertained about possible risks of becoming affected or of having affected children. If selective abortion was possible as in Tay-Sachs disease there would also be an increased demand for resources for antenatal diagnosis.

In cases where large amounts of data were collected it might be considered essential to computerise the information so that it could be used effectively. Any such scheme would require skilled staff at least initially.

b) Cost

For some diseases where therapy became available the cost of treatment might be so great that it would not be possible to treat many individuals. For example in phenylketonuria the special diet can be relaxed by the age of 6 years but in maple syrup urine disease there is no indication that dietary restriction can ever be relaxed and the treatment is thus very expensive. The effective treatment of Fabry's disease requires purified enzyme which is costly to produce.

The cost of screening might also render it uneconomical. In the U.S.A. Tay-Sachs disease occurs in 1 in 6000 Jewish births. It is

feasible to screen the 'at risk' population to detect couples where husband and wife are both carriers and monitor pregnancies of these couples. However the incidence of Pompe's disease is only 1 in 400,000 live births (Sotos and Boggs (1970)) and although heterozygote detection and antenatal diagnosis are possible widespread screening would probably not be feasible. The cost of prevention of the birth of an affected individual would have to be weighed against the cost of caring for the individual if he was born.

c) Misuse of information

Any information obtained about a person's genotype might be used to his detriment unless steps were taken to limit access to it. For example it might prove difficult to reassure the public that even though carriers might be at risk of having an affected child they themselves are quite normal. Culliton (1972a) reports that as a result of screening for the sickle cell trait in U.S.A. Blacks some carriers are allegedly having trouble obtaining life and health insurance and are being discriminated against with respect to jobs. The same might occur if individuals at risk of developing late onset dominant conditions such as Huntington's chorea were identified.

d) Unforeseen consequences

Some consequences of the introduction of these practices might only become apparent at a later date. For example treated individuals, though not at risk of having offspring with the same disease might still have abnormal offspring. It is well known that women with phenylketonuria are more likely than other women to have offspring with mental retardation or structural abnormalities. This is thought to be due to intrauterine exposure to abnormal concentrations of phenylalanine

metabolites (Howell and Stevenson, 1971). There is a high risk that fetuses of diabetic mothers will die in late pregnancy unless they are delivered prematurely. It is possible that similar phenomena might be found in other diseases.

If AI was used to any great extent it would probably be difficult to screen donors for deleterious alleles. Women using this donor sperm might then have abnormal offspring and bring the scheme into disrepute.

Some alleles which produce disease in homozygotes might have beneficial effects in the heterozygous state as yet unknown. A reduction in the frequency of such alleles might have a detrimental effect in certain populations. For example in cystic fibrosis the gene frequency is too high to be maintained solely by mutation. It has been suggested that in diseases where the gene frequency is high, heterozygotes might have enhanced resistance to disease, otherwise improved viability or enhanced fertility (Mayo, 1970b).

e) Ethical problems

Several ethical problems arise in trying to decide what are the best interests of society in general, of particular couples and of affected individuals and unborn fetuses. These have been discussed quite extensively for example at the Fogarty International Symposium (1971). It is clear that there are several different views as to what is morally acceptable which will be hard to reconcile in practice.

If an effective treatment was introduced for a disease which was previously fatal in infancy few would argue that such a treatment should be withheld because of a possible increase in gene frequency in future generations. However the situation would be somewhat different if the

treatment involved the individual in much suffering. Since the development of the ventriculoatrial shunt many hydrocephalic babies with spina bifida have been treated. However in many cases the quality of survival is less satisfactory than hoped for and many children have to undergo repeated hospital admissions. Many, including parents would prefer that such babies be allowed to die peacefully in infancy if they would still suffer from major handicaps.

If selective abortion was possible in a disease where affected individuals underwent much suffering it might be considered in the best interests of the fetus, his parents and society in general to abort affected fetuses. However in some diseases such as Downs syndrome it is difficult to say if the affected individual really does suffer himself even though a great burden is inflicted on the parents and on society in bringing up the child. Similarly if unaffected carriers could be identified in utero it might be considered in the best interests of society that they should be aborted in order to reduce the frequency of the deleterious allele even though the child would be completely normal. In either of these two latter cases the decision whether to carry out an abortion would be more difficult.

Other problems would arise if large scale screening programs were introduced in certain areas for the detection of preclinical cases of a disease or of heterozygous carriers. The identification of such individuals might point to other family members outwith the area who were at high risk of becoming affected or of having an affected child. The identified individual might however wish that his status be kept secret and there would be a conflict between his rights and those of his relatives. If individuals at high risk of having an affected child

were detected it might be in the best interests of society for them not to reproduce. However is the right of society to prevent the birth of affected children greater than the right of particular couples to have their own children? The general conclusion of the Fogarty Symposium was that society's interests are secondary to those of the individual.

At present, with little use of the practices, these problems are not faced by many people. However they are likely to become more important in the future and individuals faced with them will need some guidance as to how to act in different situations.

Conclusions and recommendations

The results of this study suggest that the joint effect of the practices discussed is likely to be a decrease in the incidence of genetic disease in the next generation. Possible exceptions might be AD diseases if therapy was to become available and AR diseases where there was a persistence of heterozygote advantage.

In the longer term the change in disease incidence would probably depend upon whether effective therapy was available for affected individuals. The papers discussed in the literature review suggest that couples are more reluctant to adopt one of the other practices if effective therapy is available or if affected individuals usually die very young. Effective therapy would have little long term effect on the incidence of AR diseases but could cause a relatively large increase in incidence of AD and XR diseases unless treated individuals voluntarily had fewer offspring.

At present none of the practices are very important in causing changes in disease incidence because they are not feasible for many

diseases and few individuals are counselled regarding their risks. The initiative for counselling is usually left to the individual himself who often only seeks counselling after having an affected child. If the child's diagnosis is late the couple may not be detected until their family is complete.

In order to alleviate distress in particular families and to reduce the incidence of genetic diseases in general there is a need for:-

i) Education - the lay-public and in particular general practitioners should be given more information about genetic diseases so that if a disease occurred in a family they would be more aware of possible implications for other family members. This might be partially achieved if genetics was more widely taught in schools so that more individuals would understand the hereditary nature of certain diseases.

ii) Screening - In order to detect more individuals at risk prospectively screening of the general population would be required at least in AR diseases. It might only be economically feasible to do this in conditions where it is relatively cheap and easy to detect heterozygotes. Or in populations where certain diseases are very common. In other, rarer, diseases heterozygote detection might not be feasible except for relatives of affected individuals or in consanguineous marriages.

iii) Extension of counselling services and follow-up - With an increase in the number of individuals ascertained there is an increased need for facilities so that they can be given genetic counselling. There is also a need for follow-up of these individuals and, in AD and XR diseases, of their relatives, to detect those at high risk.

iv) Legislation - In the future new laws might be necessary to protect the rights of certain individuals; in particular to ensure that any information gathered is not misused. Discussion is needed regarding possible legislation so that society will be prepared in advance for any increase in the use of these practices.

v) Continued reappraisal of practices - There would later be a need for follow-up of individuals adopting the practices in order to detect any unforeseen consequences such as those discussed in (d) above.

With these facilities there would be a possibility of long term decreases in the incidence of genetic diseases at least in those conditions for which there was no effective therapy where individuals at risk would be more likely to avoid having affected offspring. In diseases where therapy was cheap and effective possible longer term increases in incidence might not be important. In diseases for which therapy was expensive any increase in disease incidence would place a great burden on society. Although the increase in incidence of any particular disease might be small the joint effect might be large. In these diseases it would be in the best interests of society to advise couples at risk not to have offspring.

I personally believe that genetic counselling must be firstly devoted to the interests of particular individuals and that it would not be right to introduce laws forbidding particular couples to have offspring. I believe that with sufficient education couples would take responsible decisions regarding parenthood. If they did so relatively small reductions in fertility would be sufficient to offset the dysgenic effects of improved treatments in AR diseases. In AD and XR diseases longer term increases in gene frequency could be offset

by larger reductions in the fertility of heterozygotes or in the latter case by a reduction in fertility of affected males. In MF diseases changes in incidence could be offset by small reductions in fertility of individuals at high liability to the disease.

APPENDIX 1

DERIVATION OF CHANGES IN DISEASE INCIDENCE AND GENE FREQUENCY FOR CASES NOT CONSIDERED IN SECTION 5

In this appendix calculations of the effects of the practices not considered in section (5) are described for diseases with AR, AD (with complete penetrance), XR and MF modes of inheritance. For AD diseases with incomplete penetrance the effects of all practices are calculated. The methods of derivation of the changes are given in detail for early onset diseases and necessary modifications to the formulae for diseases of late onset are then discussed.

ONSET AGE (a)

1) AR diseases

(A) Dysgenic practices

Selection of mate (2)

Suppose a proportion w_{Aa} of heterozygotes is ascertained before marriage and a proportion c_i of these subsequently seek a marriage partner who is homozygous normal. The frequency of heterozygous couples is then approximately $4p^2q^2(1-w_{Aa}c_i)^2 \doteq 4q^2(1-w_{Aa}c_i)^2$

(i) Disease incidence Following the method for practice (4) in section (5B) the approximate net change in disease incidence is $-q^2w_{Aa}c_i(2-w_{Aa}c_i)$

(ii) Gene frequency Assuming that all individuals are able to find a marriage partner the only loss of a genes from the gene pool is by selection against aa individuals born. Therefore after subtracting the effect of natural selection the approximate net

change in gene frequency is

$$-s_{aa}q^2 (1-w_{Aa}c_i)^2 + s_{aa}q^2 = q^2 s_{aa} w_{Aa} c_i (2-w_{Aa}c_i)$$

Selective abortion with reproductive compensation (3)

- retrospective

Suppose heterozygous couples are ascertained retrospectively. The changes in disease incidence and gene frequency are equal to those which occur for prospective ascertainment multiplied by P_r (the proportion of offspring born after the first affected child).

(B) Eugenic practices

Family limitation by carriers at risk (5)

- prospective

Suppose a proportion w_m of heterozygous couples is ascertained prospectively and of these a proportion c_m subsequently reduce their intended family size by a proportion f'_m. Putting these terms together the fitness of heterozygous couples is $(1-w_m c_m f'_m)$. The changes in disease incidence and gene frequency can be derived by following the method for practice (4) in section (5B).

(i) Disease incidence The approximate net change in disease incidence is $q^2 (1-w_m c_m f'_m) - q^2 + 2q^3 s_{aa} \doteq -q^2 w_m c_m f'_m$

(ii) Gene frequency Since one half of the genes contributed by heterozygous couples are a the reduction in gene frequency due to family limitation is approximately $\frac{1}{2} \cdot 4p^2 q^2 w_m c_m f'_m \doteq 2q^2 w_m c_m f'_m$ The reduction in gene frequency due to selection against affected individuals born is approximately $s_{aa} q^2 (1-w_m c_m f'_m)$

Therefore the net change in gene frequency due to the practice is approximately $-2q^2 w_m c_m f'_m - s_{aa} q^2 (1-w_m c_m f'_m) + s_{aa} q^2 = -q^2 w_m c_m f'_m (2-s_{aa})$

- retrospective

If heterozygous couples are ascertained retrospectively the changes in disease incidence and gene frequency are equal to those calculated above multiplied by P_r.

Family limitation by sibs of affected individuals (6)

P_s is the proportion of the offspring of heterozygous couples who are normal sibs of affected individuals. In the grandparental generation the frequency of these couples is approximately $4p^2q^2$. Therefore in the parental generation at birth the proportion of individuals who are normal sibs of affected individuals is $4p^2q^2P_s$. Two-thirds of these are heterozygotes therefore the proportion of all heterozygotes in the parental generation at birth who are sibs of affected individuals is $\frac{2}{3} \cdot 4p^2q^2P_s/2pq \doteq \frac{4}{3}qP_s$.

Suppose a proportion w_{Aa} of these heterozygotes is ascertained prospectively and a proportion c_i of these subsequently reduce their intended family size by a proportion f'_{Aa}. Putting these terms together the fitness of heterozygotes is approximately $(1-\frac{4}{3}q P_s w_{Aa} c_i f'_{Aa})$.

Let $H = \frac{4}{3} P_s w_{Aa} c_i f'_{Aa}$ so that the fitness of heterozygotes is $(1-qH)$.

(i) Disease incidence Heterozygotes with an affected sib make up a very small proportion of all heterozygotes. The number of offspring born to affected individuals is not negligible compared with the number born to their normal sibs. Matings involving affected individuals must therefore be considered. These could be ignored in the calculations

of changes when a proportion of all heterozygotes or of heterozygous couples adopted a practice. Couples at risk of having affected offspring have the following frequencies and fitnesses:-

Mating type	Frequency	Fitness	Proportions of offspring		
			AA	Aa	aa
Aa x Aa	$4p^2q^2$	$(1-qH)^2$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
Aa x aa	$4pq^3$	$(1-qH)(1-s_{aa})$	0	$\frac{1}{2}$	$\frac{1}{2}$
aa x aa	q^4	$(1-s_{aa})^2$	0	0	1

The incidence of affected individuals in the offspring is approximately

$$\frac{1}{4}.\ 4p^2q^2\ (1-qH)^2 + \frac{1}{2}.\ 4pq^3\ (1-qH)(1-s_{aa}) + q^4\ (1-s_{aa})^2 \doteq q^2 - 2\ s_{aa}q^3 - 2q^3H$$

Subtracting the incidence in the parental generation and the effect of natural selection the net change due to the practice is approximately

$$-\frac{8}{3}\ q^3 P_s w_{Aa} c_i f'_{Aa}$$

(ii) Gene frequency Following the method for practice (4) in section (5B) the reduction in gene frequency due to family limitation is approximately $\frac{1}{2}.\ 2pq.qH \doteq q^2H$. The reduction in gene frequency due to selection against affected individuals born is approximately $s_{aa}\ (q^2 - 2s_{aa}q^3 - 2q^3H)$.

Therefore the net change in frequency due to the practice is approximately

$$-\frac{4}{3}\ q^2 P_s w_{Aa} c_i f'_{Aa}$$

Artificial insemination for spouses of carrier males (7)

Suppose a proportion w_{Aa} of heterozygous carrier males is ascertained prospectively and the spouses of a proportion c_i of these are inseminated by donor sperm. Heterozygous couples have frequencies as follows:-

	Mating type	Frequency	Proportions of offspring		
			AA	Aa	aa
Practising AI	Aa x Aa	$4p^2q^2w_{Aa}c_i$	$\frac{1}{2}$	$\frac{1}{2}$	0
Not practising AI	Aa x Aa	$4p^2q^2(1-w_{Aa}c_i)$	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$

(i) Disease incidence Following the same method as for practice (4) in section (5B) the approximate net change in disease incidence is $q^2(1-w_{Aa}c_i) - q^2 + 2q^3s_{aa} \doteq -q^2w_{Aa}c_i$

(ii) Gene frequency A proportion $w_{Aa}c_i$ of heterozygous males do not transmit genes to the next generation if their spouses are inseminated by donor sperm. One half of heterozygotes are male and half their genes are a. This practice therefore results in a reduction in gene frequency of approximately $\frac{1}{2}.\ 2pq\ \frac{1}{2}.w_{Aa}c_i \doteq \frac{q}{2}w_{Aa}c_i$

The reduction in gene frequency due to selection against affected individuals born is approximately $s_{aa}q^2(1-w_{Aa}c_i)$

Therefore the approximate net change in gene frequency due to the practice is $-\frac{q}{2}w_{Aa}c_i - s_{aa}q^2(1-w_{Aa}c_i) + s_{aa}q^2 \doteq -\frac{q}{2}w_{Aa}c_i$

Artificial insemination for spouses of carrier males at risk (8)

- prospective

Suppose a proportion w_m of heterozygous couples is ascertained prospectively and a proportion c_m of these practise AI using donor sperm. The frequency of couples using AI is then $4p^2q^2w_mc_m$

(i) Disease incidence By the same method as above the approximate net change in disease incidence is $-q^2w_mc_m$

(ii) Gene frequency If heterozygous couples do not practise AI one half of the genes in their offspring are a. If they practise AI only one quarter of the genes are a. Therefore the reduction in gene frequency due to AI is approximately $4p^2q^2w_mc_m\left[\frac{1}{2} - \frac{1}{4}\right] \doteq q^2w_mc_m$
The reduction in gene frequency due to selection against affected individuals born is approximately $s_{aa}q^2(1-w_mc_m)$
Therefore the approximate net change in gene frequency due to the practice is $-q^2w_mc_m - s_{aa}q^2(1-w_mc_m) + s_{aa}q^2 = -q^2w_mc_m(1-s_{aa})$

- retrospective

If heterozygous couples are ascertained retrospectively the changes in disease incidence and gene frequency are equal to those calculated above multiplied by P_r.

Selective abortion without reproductive compensation (9)

- prospective

Suppose a proportion w_m of couples where both partners are heterozygous is ascertained prospectively and a proportion c_m of these practise selective abortion of affected fetuses but without compensation.

Family size is therefore reduced.

(i) Disease incidence The net change in disease incidence is the same as for reproductive compensation (3).

(ii) Gene frequency The net change in gene frequency is the same as for reproductive compensation except that there is no increase in gene frequency due to the birth of additional heterozygotes. The net change is therefore approximately

$$-s_{aa}q^2(1-w_m c_m) - q^2 w_m c_m + q^2 s_{aa} = -q^2 w_m c_m (1-s_{aa})$$

- retrospective

If heterozygous couples are ascertained retrospectively the changes are equal to those calculated above multiplied by P_r.

2a) AD diseases with complete penetrance

(A) Dysgenic practices

Selection of mate (2)

This practice is not relevant to AD diseases as all carriers of the deleterious allele are at risk of having an affected child no matter what is the genotype of their mate.

Selection abortion with reproductive compensation (3)

- retrospective

Suppose a proportion w_m of couples where one partner is affected is ascertained retrospectively and a proportion c_m of these practise selective abortion of affected fetuses with reproductive compensation.

The changes in disease incidence and gene frequency are equal to those when there is prospective ascertainment multiplied by P_r.

(B) Eugenic practices

Family limitation by carriers at risk (5)

- prospective

All heterozygous carriers of the deleterious allele are at risk of having affected offspring. The changes in disease incidence and gene frequency are therefore identical to those calculated for practice (4) in section (5B).

- retrospective

If couples where one partner is affected are ascertained after the birth of an affected child the changes in disease incidence and gene frequency are equal to those for practice (4) multiplied by P_r.

Family limitation by sibs of affected individuals (6)

In AD diseases where there is complete penetrance none of the normal sibs of affected individuals are carriers of the deleterious allele and so if they restrict their family size there is no change in disease incidence or in gene frequency.

Artificial insemination for spouses of carrier males (7)

Suppose a proportion w_{A-} of heterozygous (affected) males is ascertained prospectively and the spouses of a proportion c_i of these are inseminated by donor sperm. Couples where one partner is affected

have frequencies as follows:-

Mating type Male	Female	Frequency	Fitness	Proportions of offspring Aa	aa
Practising AI	Aa x aa	$2p^3qw_{A-}c_i$	$(1-s_{A-})$	0	1
Not practising AI	Aa x aa	$2p^3q(1-w_{A-}c_i)$	$(1-s_{A-})$	$\frac{1}{2}$	$\frac{1}{2}$
Not practising AI	aa x Aa	$2p^3q$	$(1-s_{A-})$	$\frac{1}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $q(1-s_{A-})\ (2-w_{A-}c_i)$

Subtracting the incidence in the parental generation and the effect of natural selection the approximate net change due to the practice is $-qw_{A-}c_i\ (1-s_{A-})$

(ii) Gene frequency Following the same method as for AR diseases the reduction in gene frequency due to carrier males not transmitting genes to the next generation is approximately

$\frac{1}{2}.\ 2pq\ (1-s_{A-})\ \frac{1}{2}.\ w_{A-}c_i \doteq \frac{q}{2}w_{A-}c_i\ (1-s_{A-})$

The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2}\ s_{A-}q\ (1-s_{A-})(2-w_{A-}c_i)$

Therefore the net change in gene frequency due to the practice is approximately $-\frac{q}{2}\ w_{A-}c_i\ (1-s_{A-}) - \frac{1}{2}\ s_{A-}q\ (1-s_{A-})\ (2-w_{A-}c_i) + q\ s_{A-}\ (1-s_{A-})$

$\doteq -\frac{q}{2}\ w_{A-}c_i\ (1-s_{A-})^2$

Artificial insemination for spouses of carrier males at risk (8)

- prospective

Since all heterozygous carrier males are at risk of having affected

offspring the changes for this practice are identical to those calculated for (7) above.

- retrospective

If couples are ascertained after the birth of an affected child the changes are equal to those calculated for (7) above multiplied by P_r.

Selective abortion without reproductive compensation (9)

- prospective

Suppose a proportion w_m of couples where one partner is affected is ascertained prospectively and a proportion c_m of these practise selective abortion but without reproductive compensation so that family size is reduced. The changes in disease incidence and gene frequency are identical to those when there is reproductive compensation. This is because in the latter case none of the offspring born to compensate for affected individuals carry the A gene.

- retrospective

The changes in disease incidence and gene frequency are identical to those when there is reproductive compensation.

2b) AD diseases with incomplete penetrance

(A) Dysgenic practices

Improved treatment (1)

Suppose an improved treatment for the disease reduces selection

against affected individuals by an amount s'_{A-}. The disease incidence and gene frequency changes are calculated by the same method as used in section (5A) and the effect of existing forces is subtracted.

(i) Disease incidence The change in disease incidence between parental and offspring generations is $-2qy^2 (s_{A-}-s'_{A-})$. Subtracting the effect of natural selection the net change due to the practice is approximately $2qy^2 s'_{A-}$

(ii) Gene frequency Similarly the approximate change in gene frequency between parental and offspring generations is

$-qy(s_{A-}-s'_{A-}) (1-y(s_{A-}-s'_{A-}))$.

Subtracting the effect of natural selection the approximate net change in gene frequency due to the practice is $qys'_{A-}(1-2ys_{A-}+ys'_{A-})$.

However, for the same reasons as for AD diseases with complete penetrance it is more valid to compare the proportionate changes in the frequency of A between parental and offspring generations. Without improved treatment the proportionate change is $-qys_{A-}(1-ys_{A-})/q(1-ys_{A-}) = -ys_{A-}$.

Similarly with improved treatment the proportionate change is

$-y(s_{A-}-s'_{A-})$.

Therefore the net effect of improved treatment is to diminish the proportionate reduction in gene frequency by an amount ys'_{A-}.

Selection of mate (2)

As for diseases with complete penetrance this practice is not relevant.

Selective abortion with reproductive compensation (3)

- prospective

Suppose a proportion w_m of couples, where one partner is affected, is ascertained and a proportion c_m of these practise selective abortion of heterozygous carrier fetuses with reproductive compensation. It is assumed that the fetuses aborted are those where the deleterious gene is penetrant and therefore are all affected. This is not the case if fetuses are aborted who are likely to be carriers of the deleterious allele because of their genotype at a linked locus. In the latter case some heterozygotes aborted are not affected. The reduction in disease incidence and the increase in gene frequency, calculated on these assumptions are however the maxima which could occur. This is because all the carriers aborted are affected and therefore at a selective disadvantage and any born to compensate for them have normal fitness. Couples where one partner is a heterozygote have frequencies and fitnesses as follows:-

	Frequency	Fitness	Proportions of offspring		
			Aa		aa
One partner affected			Affected	Normal	
Practising selective abortion	$4p^3qyw_m c_m$	$(1-s_{A-})$	0	$\frac{1-y}{2-y}$	$\frac{1}{2-y}$
Not practising selective abortion	$4p^3qy(1-w_m c_m)$	$(1-s_{A-})$	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$
Neither partner affected					
Not practising selective abortion	$4p^3q(1-y)$	1	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{y}{2}.\ 4p^3q\ [y(1-w_m c_m)(1-s_{A-}) + (1-y)]$

$$\doteq 2qy\ (1-ys_{A-}-w_m c_m y+w_m c_m y s_{A-})$$

Subtracting the disease incidence in the parental generation and the effect of natural selection the net change in disease incidence due to the practice is $\doteq -2qy^2 w_m c_m (1-s_{A-})$

(ii) Gene frequency The reduction in gene frequency due to abortion of affected fetuses, half of whose genes are A, is approximately

$$4p^3 qy w_m c_m\ (1-s_{A-}).\ \frac{y}{2}.\ \frac{1}{2} \doteq qy^2 w_m c_m\ (1-s_{A-})$$

The reduction in gene frequency due to selection against affected individuals born is approximately $2qy\ (1-ys_{A-}-w_m c_m y+w_m c_m s_{A-} y).\ \frac{1}{2} s_{A-}$

$$\doteq qys_{A-}(1-ys_{A-}-w_m c_m y+w_m c_m y s_{A-})$$

To compensate for affected fetuses aborted there are $2qy^2 w_m c_m (1-s_{A-})$ individuals born. A proportion $[\frac{1}{2}(1-y)]/[\frac{1}{2}+\frac{1}{2}(1-y)] = (1-y)/(2-y)$ are unaffected carriers. The approximate increase in gene frequency due to the birth of additional unaffected carriers is therefore $qy^2 w_m c_m\ (1-y)(1-s_{A-})/(2-y)$.

Subtracting the effect of natural selection the approximate net change in gene frequency becomes

$$-qy^2 w_m c_m\ \frac{(1-s_{A-})(1-2s_{A-}+ys_{A-})}{(2-y)}$$

- retrospective

Suppose a proportion w_m of all couples, where one partner is heterozygous and who have had an affected child, is ascertained and that a proportion c_m of these subsequently practise selective abortion

of affected fetuses with reproductive compensation. When there is prospective detection ascertainment is assumed to be dependent on one parent being affected. When detection is retrospective it is only dependent on the child being affected. P_r is the proportion of offspring born to couples, where one partner is a heterozygote, after the first affected child. If there is selective abortion with reproductive compensation these couples will have the following proportions of offspring:-

affected heterozygotes $(1-w_m c_m P_r)y/2$

normal heterozygotes $\frac{1-y}{2} + \frac{(1-y)}{(2-y)} \cdot \frac{y}{2} w_m c_m P_r = \frac{1-y}{2}\left[1 + w_m c_m P_r \cdot \frac{y}{2-y}\right]$

normal homozygotes $\frac{1}{2} + \frac{1}{(2-y)} \cdot \frac{y}{2} \cdot w_m c_m P_r = \frac{1}{2}\left[1 + w_m c_m P_r \cdot \frac{y}{2-y}\right]$

This is summarised in the table below

Mating type	Frequency	Fitness	Proportions of offspring		
			Aa		aa
			Affected	Normal	
Aa x aa	$4p^3q$	$(1-ys_{A-})$	$\frac{y}{2}[1-w_m c_m P_r]$	$\frac{(1-y)}{2}[1+w_m c_m P_r \cdot \frac{y}{2-y}]$	$\frac{1}{2}[1+w_m c_m P_r \cdot \frac{y}{2-y}]$

(i) Disease incidence The disease incidence in the offspring is approximately $4p^3q\,(1-ys_{A-})\,\frac{y}{2}\,(1-w_m c_m P_r) \doteq 2qy\,(1-ys_{A-})\,(1-w_m c_m P_r)$
As before, subtracting the disease incidence in the parental generation and the effect of natural selection the approximate net change in disease incidence due to the practice becomes $-2qyw_m c_m P_r\,(1-ys_{A-})$

(ii) Gene frequency Following the method of calculation for prospective ascertainment the reduction in gene frequency due to selective abortion of affected fetuses is approximately $qyw_m c_m P_r\,(1-ys_{A-})$
The reduction in gene frequency due to selection against affected

individuals born is approximately $qys_{A-}(1-ys_{A-})(1-w_m c_m P_r)$

The increase in gene frequency due to the birth of additional unaffected carriers is $qyw_m c_m P_r \frac{(1-y)(1-ys_{A-})}{2-y}$

The approximate net change in gene frequency is therefore

$$-qyw_m c_m P_r(1-ys_{A-}) - qys_{A-}(1-ys_{A-})(1-w_m c_m P_r) + \frac{qyw_m c_m P_r(1-y)(1-ys_{A-})}{2-y}$$

$$+ qys_{A-}(1-ys_{A-})$$

$$= -qyw_m c_m P_r \frac{(1-ys_{A-})(1-2s_{A-}+ys_{A-})}{(2-y)}$$

(B) Eugenic practices

Family limitation by carriers (4)

- prospective

Suppose a proportion w_{A-} of affected heterozygotes is ascertained prospectively and of these a proportion c_i reduce the number of offspring they would have had subsequently by a proportion f'_{A-}. Couples where one partner is a heterozygote have frequencies and fitnesses as follows:-

	Frequency	Fitness	Proportions of offspring		
			Aa		aa
			Affected	Normal	
One partner affected	$4p^3qy$	$(1-w_{A-}c_i f'_{A-})(1-s_{A-})$	$\frac{y}{2}$	$\frac{1-y}{2}$	$\frac{1}{2}$
Neither partner affected	$4p^3q(1-y)$	1	$\frac{y}{2}$	$\frac{1-y}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $\frac{y}{2}.\ 4p^3q\ [y(1-w_{A-}c_i f'_{A-})(1-s_{A-}) + (1-y)]$

$$\doteq 2qy\ [1-y\ (s_{A-}+w_{A-}c_i f'_{A-}-s_{A-}w_{A-}c_i f'_{A-})]$$

After subtracting the incidence in the parental generation and the effect of natural selection the net change due to the practice is approximately $-2qy^2 w_{A-} c_i f'_{A-} (1-s_{A-})$

(ii) Gene frequency The reduction in gene frequency due to family limitation is approximately $2pqy (1-s_{A-}) w_{A-} c_i f'_{A-} \cdot \frac{1}{2} \doteq qyw_{A-} c_i f'_{A-} (1-s_{A-})$ The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2} s_{A-} \cdot 2qy[1-y (s_{A-} + w_{A-} c_i f'_{A-} - s_{A-} w_{A-} c_i f'_{A-})]$ After subtracting the effect of natural selection the approximate net change due to the practice is $-qyw_{A-} c_i f'_{A-} (1-s_{A-}) (1-ys_{A-})$

Family limitation by carriers at risk (5)

- prospective

As in the case of diseases with complete penetrance all heterozygous carriers are at risk of having affected offspring. If only affected heterozygotes are ascertained the changes are the same as those calculated for (4) above.

- retrospective

Suppose a proportion w_{A-} of all heterozygous carriers who have had an affected child is ascertained and of these a proportion c_i reduce the number of offspring they would have had subsequently by a proportion f'_{A-}. Couples where one partner is heterozygous have frequency and fitness as follows: -

Mating type	Frequency	Fitness	Proportions of offspring		
			Aa		aa
			Affected	Normal	
Aa x aa	$4p^3q$	$(1-ys_{A-})(1-w_{A-}c_if'_{A-}P_r)$	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$

The changes in disease incidence and gene frequency are calculated as in (4) above.

(i) Disease incidence The disease incidence in the offspring is approximately $2qy(1-ys_{A-})(1-w_{A-}c_if'_{A-}P_r)$. The approximate net change in incidence is therefore $-2qyw_{A-}c_if'_{A-}P_r(1-ys_{A-})$

(ii) Gene frequency The reduction in gene frequency due to family limitation is approximately $qw_{A-}c_if'_{A-}P_r(1-ys_{A-})$
The reduction in gene frequency due to selection against affected individuals born is approximately $qys_{A-}(1-ys_{A-})(1-w_{A-}c_if'_{A-}P_r)$
The approximate net change in gene frequency due to the practice is therefore $-qw_{A-}c_if'_{A-}P_r(1-ys_{A-})^2$

Family limitation by sibs of affected individuals (6)

A proportion P_s of the offspring of couples where one partner is a heterozygous carrier are normal sibs of affected individuals. In the grandparental generation the frequency of these couples is approximately $4p^3q$. Therefore in the parental generation at birth the proportion of individuals who are normal sibs of affected individuals is $4p^3qP_s$. Of these a proportion $\frac{(1-y)}{(2-y)}$ are unaffected carriers of the deleterious allele. Therefore the proportion of all unaffected carriers in the parental generation at birth who are normal sibs of affected individuals is

$$4p^3qP_s\,\frac{(1-y)}{(2-y)} \Big/ 2pq(1-y) \doteq \frac{2\,P_s}{2-y}$$

Suppose a proportion w_{A-} of these unaffected carriers is ascertained prospectively and a proportion c_i of these subsequently reduce their intended family size by a proportion f'_{A-}. Putting these terms together the fitness of unaffected carriers is approximately $(1 - \frac{2P_s}{2-y} \cdot w_{A-}c_i f'_{A-})$.

Couples where one partner is heterozygous have the following frequencies and fitnesses:-

	Frequency	Fitness	Proportions of offspring		
			Aa		aa
			Affected	Normal	
One partner affected	$4p^3qy$	$(1-s_{A-})$	$\frac{y}{2}$	$\frac{1-y}{2}$	$\frac{1}{2}$
Neither partner affected	$4p^3q(1-y)$	$[1 - \frac{2P_s w_{A-} c_i f'_{A-}}{2-y}]$	$\frac{y}{2}$	$\frac{1-y}{2}$	$\frac{1}{2}$

The changes in disease incidence and gene frequency are calculated as in (4) above.

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $2qy\,[1-ys_{A-} - \frac{2P_s w_{A-} c_i f'_{A-}\,(1-y)]}{(2-y)}$

The approximate net change due to the practice is therefore

$$\frac{-4qyP_s w_{A-} c_i f'_{A-}(1-y)}{(2-y)}$$

(ii) Gene frequency The reduction in gene frequency due to family limitation is approximately $\frac{2qP_s w_{A-} c_i f'_{A-}(1-y)}{(2-y)}$

The reduction in gene frequency due to selection against affected individuals born is approximately $qys_{A-}[1-ys_{A-}-2P_s w_{A-} c_i f'_{A-} \frac{(1-y)}{(2-y)}$

The approximate net change due to the practice is therefore

$$-2qP_s w_{A-} c_i f'_{A-} \frac{(1-y)(1-ys_{A-})}{(2-y)}$$

Artificial insemination for spouses of carrier males (7)

Suppose a proportion w_{A-} of affected heterozygotes is ascertained prospectively and the spouses of a proportion c_i of these are inseminated by donor sperm. Couples where one partner is a heterozygote have frequencies and fitnesses as follows:

	Mating type Male	Female	Frequency	Fitness	Proportions of offspring Aa		aa
One partner affected					Affected	Normal	
Practising AI	Aa	aa	$2p^3qyw_{A-}c_i$	$(1-s_{A-})$	0	0	1
Not practising AI	Aa	aa	$2p^3qy(i-w_{A-}c_i)$	$(1-s_{A-})$	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$
Not practising AI	aa	Aa	$2p^3qy$	$(1-s_{A-})$	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$
Neither partner affected							
Not practising AI	Aa aa	aa Aa	$4p^3q(1-y)$	1	$\frac{y}{2}$	$\frac{(1-y)}{2}$	$\frac{1}{2}$

(i) Disease incidence The approximate incidence of affected individuals in the offspring is $qy(2-w_{A-}c_i y - 2ys_{A-}+yw_{A-}c_i s_{A-})$

Subtracting the disease incidence in the parental generation and the effect of natural selection the approximate net change in incidence due to the practice is $-qy^2 w_{A-} c_i (1-s_{A-})$

(ii) Gene frequency The reduction in gene frequency because affected males do not transmit A alleles to the next generation is approximately $\frac{1}{2}$. $pqy(1-s_{A-})w_{A-}c_i \doteq \frac{1}{2} qyw_{A-}c_i(1-s_{A-})$

The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2} s_{A-}qy(2-w_{A-}c_iy - 2ys_{A-}+yw_{A-}c_is_{A-})$

Subtracting the effect of natural selection the approximate net change in gene frequency becomes $-\frac{1}{2} qyw_{A-}c_i (1-s_{A-})(1-ys_{A-})$

Artificial insemination for spouses of carrier males at risk (8)

- prospective

Since all heterozygous affected carrier males are at risk of having affected offspring the changes for this practice are the same as those calculated for (7) above.

- retrospective

Suppose a proportion w_{Aa} of all heterozygous carriers who have had an affected child is ascertained and the spouses of a proportion c_i of these are inseminated by donor sperm. Couples where one partner is a heterozygote have frequencies and fitnesses as follows:

Mating type		Frequency	Fitness	Proportions of offspring		
Male	Female			Aa Affected	Aa Normal	aa
Aa x aa		$2p^3q$	$(1-ys_{A-})$	$\frac{y}{2}(1-w_{A-}c_iP_r)$	$\frac{1-y}{2}(1-w_{A-}c_iP_r)$	$\frac{1}{2}(1+w_{A-}c_iP_r)$
aa x Aa		$2p^3q$	$(1-ys_{A-})$	$\frac{y}{2}$	$\frac{1-y}{2}$	$\frac{1}{2}$

The changes in disease incidence and gene frequency are calculated in the same way as in (7) above.

(i) Disease incidence The approximate incidence of affected individuals in the offspring is

$$2p^3q(1-ys_{A-})\left[\frac{y}{2}(1-w_{A-}c_iP_r)+\frac{y}{2}\right] \doteq qy(1-ys_{A-})(2-w_{A-}c_iP_r)$$

The approximate net change in incidence due to the practice is therefore

$$-qyw_{A-}c_iP_r(1-ys_{A-})$$

(ii) Gene frequency The reduction in gene frequency because heterozygous males do not transmit genes to the next generation is approximately $\frac{1}{2}qw_{A-}c_iP_r(1-ys_{A-})$

The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{2}s_{A-}qy(1-ys_{A-})(2-w_{A-}c_iP_r)$

The approximate net change in gene frequency is therefore

$$-\frac{1}{2}qw_{A-}c_iP_r(1-ys_{A-})^2$$

Selective abortion without reproductive compensation (9) - prospective

Suppose a proportion w_m of couples, where one partner is affected, is ascertained and a proportion c_m of these practise selective abortion of affected fetuses but without reproductive compensation.

(i) Disease incidence The net change in disease incidence is the same as that when there is reproductive compensation.

(ii) Gene frequency The net change in gene frequency is the same as that when there is reproductive compensation except that there is no increase in gene frequency due to the birth of additional unaffected carriers. The net change is therefore approximately

$$-qy^2w_mc_m(1-s_{A-}) - qys_{A-}(1-ys_{A-} - w_mc_my + w_mc_mys_{A-}) + qys_{A-}(1-ys_{A-})$$

$$\doteq -qy^2w_mc_m(1-s_{A-})^2$$

- retrospective

Suppose a proportion w_m of all couples where one partner is heterozygous and who have had an affected child is ascertained and that a proportion c_m of these subsequently practise selective abortion of affected fetuses without reproductive compensation.

(i) Disease incidence The net change in disease incidence is the same as that when there is reproductive compensation.

(ii) Gene frequency The net change in gene frequency is the same as that when there is reproductive compensation except that there is no increase in gene frequency due to the birth of additional unaffected carriers. The net change is therefore approximately

$$-qyw_m c_m P_r(1-ys_{A-}) - qys_{A-}(1-ys_{A-})(1-w_m c_m P_r) + qys_{A-}(1-ys_{A-})$$

$$\doteq -qyw_m c_m P_r(1-ys_{A-})(1-s_{A-})$$

3) XR diseases

(A) Dysgenic practices

Selection of male (2)

This practice is not relevant to XR diseases as all heterozygous carrier females are at risk of having an affected child no matter what is the genotype of their mate.

Selective abortion with reproductive compensation (3)

- retrospective

Suppose a proportion w_m of couples where the female is a carrier is ascertained retrospectively and a proportion c_m of these subsequently

practise selective abortion of certain fetuses with reproductive compensation. The changes in disease incidence and gene frequency are equal to those which occur for prospective ascertainment multiplied by P_r.

(B) Eugenic practices

Family limitation by carriers at risk (5)

- prospective

All heterozygous carrier females are at risk of having affected offspring. The changes in disease incidence and gene frequency are therefore identical to those calculated for practice (4) in section (5B).

- retrospective

If heterozygous carrier females are ascertained retrospectively the changes in disease incidence and gene frequency are equal to those for practice (4) multiplied by P_r.

Family limitation by sibs of affected individuals (6)

Let P_s be the proportion of the offspring of couples, where the female is a carrier, who are normal sibs of affected individuals. In the grandparental generation the frequency of these couples is approximately $2p^2q$. Therefore in the parental generation at birth a proportion $2p^2qP_s$ individuals are normal sibs of affected individuals. The proportion of the parental generation who are carrier female sibs of affected individuals is one third of this. Half the parents are female and a proportion 2pq of them are carriers. Therefore the proportion of carrier females who are sibs of affected individuals is

approximately $2p^2qP_s \cdot \frac{1}{3} \Big/ \frac{1}{2} \cdot 2pq \doteq \frac{2}{3} P_s$

Suppose a proportion w_{Aa} of these females is ascertained prospectively and a proportion c_i of them subsequently reduce their family size by a proportion f'_{Aa}. Couples at risk of having an affected child have frequency and fitness as follows:-

Mating type	Frequency	Fitness	Proportions of offspring			
			Females		Males	
			AA	Aa	AY	aY
Aa x AY	$2p^2q$	$(1-\frac{2}{3}P_s w_{Aa} c_i f'_{Aa})$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{2}$

The changes in disease incidence and gene frequency are calculated as for practice (4) in Section (5B)

(i) Disease incidence The approximate net change in disease incidence is $-\frac{2}{3}qP_s w_{Aa} c_i f'_{Aa}$

(ii) Gene frequency The approximate net change in gene frequency is $-\frac{2}{9}qP_s w_{Aa} c_i f'_{Aa}(2-s_a)$

Artificial insemination for spouses of carrier males (7)

In XR diseases males with the deleterious allele are affected. Suppose a proportion w_a of these is ascertained and the spouses of a proportion c_i of these are inseminated by donor sperm.

(i) Disease incidence The only affected males at risk of having affected offspring are those married to carrier females. Even if their spouses are inseminated by donor sperm one half of their male offspring are affected. The disease incidence is therefore the same as when only existing forces are operating i.e. $q(1-qs_a)$.

There is therefore no change in disease incidence as a result of this practice.

(ii) Gene frequency The approximate frequency of a in the parental generation at reproduction is $q(1-\frac{1}{3}s_a)$.

As a result of AI for spouses of affected males (who contribute one third of the genes at the locus) the reduction in gene frequency is approximately $\frac{1}{3}q(1-s_a)w_a c_i$

The reduction in gene frequency due to selection against affected individuals born is approximately $\frac{1}{3}s_a q(1-qs_a)$

Subtracting the effect of natural selection the approximate net change in gene frequency due to the practice is therefore

$$-\frac{1}{3}qw_a c_i(1-s_a) - \frac{1}{3}qs_a(1-qs_a) + \frac{1}{3}qs_a = -\frac{1}{3}qw_a c_i(1-s_a)$$

Artificial insemination for spouses of carrier males at risk (8)

As stated above, affected males at risk of having affected offspring are those married to carrier females. One half of the sons of these couples would be affected even if the females were inseminated by donor sperm. This practice is therefore not relevant to XR diseases as a means of preventing the birth of affected offspring.

Selective abortion without reproductive compensation (9)

- prospective

Suppose a proportion w_m of couples where the female is a carrier is ascertained prospectively and a proportion c_m of these practise selective abortion but without reproductive compensation.

(i) Disease incidence The net change in disease incidence for cases (a), (b) and (c) is the same as for practice (3), where there is reproductive compensation.

(ii) Gene frequency The reduction in gene frequency due to selective abortion of affected male fetuses and to selection against affected individuals born is the same as when there is reproductive compensation. There are no additional heterozygous carrier females born in cases (a) and (b). Therefore the approximate net changes in gene frequency are as follows.

(a) abortion of all males

and (b) abortion of affected males

The net change in gene frequency is approximately

$$-\frac{1}{3}qs_a(1-w_m c_m) - \frac{1}{3}qw_m c_m + \frac{1}{3}qs_a = -\frac{1}{3}qw_m c_m(1-s_a)$$

(c) abortion of affected males and carrier females

The approximate net change in gene frequency is the same as that when there is reproductive compensation. This is because even in the latter case no additional offspring are born who carry the deleterious allele.

- retrospective

Suppose a proportion w_m of couples where the wife is a carrier is ascertained retrospectively and a proportion c_m of these subsequently practise selective abortion of certain fetuses without reproductive compensation. The changes in disease incidence and gene frequency are equal to those which occur for prospective ascertainment multiplied by P_r.

4) MF diseases

(A) Dysgenic practices

Selection of mate (2)

This practice is not relevant for MF diseases as several, often unknown, factors are involved in the development of these diseases and it is not possible for any individual to guarantee not to have an affected child by the choice of a particular marriage partner.

Selective abortion with reproductive compensation (3)

- retrospective

Suppose a proportion w_x of couples who have had an affected child is ascertained and of these a proportion c_m practise selective abortion of affected fetuses with reproductive compensation. If there is no selective abortion the incidence of affected individuals in the offspring is approximately $P - a^2P^2h^2s_f$ (as a result of existing forces only). If P_{rm} is the proportion of affected individuals born after the first affected child in the family then with selective abortion and reproductive compensation the disease incidence is approximately $(1-w_x c_m P_{rm})\ (P-a^2P^2h^2s_f)$.

The change in disease incidence between parental and offspring generations is therefore approximately $(1-w_x c_m P_{rm})\ (P-a^2P^2h^2s_f) - P$.

Subtracting the effect of natural selection the approximate net change in disease incidence due to the practice is $(1-w_x c_m P_{rm})(P-a^2P^2h^2s_f)$

$$- P + a^2P^2h^2s_f = -w_x c_m P_{rm}(P-a^2P^2h^2s_f)$$

(B) Eugenic practices

Family limitation by carriers at risk (5)

- prospective

Suppose it is possible to detect individuals of high liability whose spouses also have a high liability such that the mean liability of the two individuals exceeds a certain value x'' say. Suppose P_x is the proportion of couples exceeding this liability and a proportion w_x is ascertained and a proportion c_m of these subsequently reduce their intended family size by a proportion f'_m. Couples therefore have frequencies and fitnesses as below:-

	Liability not greater than x''	Liability greater than x''
Frequency	$(1-P_x)$	P_x
Mean liability	$\sqrt{2}n_x - zs_f$	$\sqrt{2}a_x - zs_f$
Fitness	1	$1-w_x c_m f'_m$

The mean liability of the offspring is therefore

$$\frac{h^2\left[(1-P_x)(\sqrt{2}n_x - zs_f) + P_x(1-w_x c_m f'_m)(\sqrt{2}a_x - zs_f)\right]}{(1-P_x) + P_x(1-w_x c_m f'_m)}$$

Following the method used in section (5A) the change in disease incidence between parental and offspring generations is approximately $z(=aP)$ times the mean liability.

Since the denominator is approximately equal to one the change in disease incidence between parental and offspring generations is approximately

$$-aPh^2\left[\sqrt{2}a_x P_x w_x c_m f'_m + aPs_f(1-w_x c_m f'_m P_x)\right]$$

Subtracting the effect of existing forces the approximate net change due to the practice is $-aPh^2 w_x c_m f'_m [\sqrt{2a_x P_x} - aPP_m s_f]$

- retrospective

Suppose a proportion w_x of couples who have had an affected child is ascertained and of these a proportion c_m reduce the number of offspring they would have had subsequently by a proportion f'_m. The change in disease incidence is calculated in a similar manner to that in (3) above.

If there is no family limitation the incidence of affected individuals in the offspring is approximately $P - a^2P^2h^2s_f$.
With family limitation the disease incidence is approximately
$(1-w_x c_m f'_m P_{rm})(P-a^2P^2h^2s_f)$
The approximate net change in disease incidence due to the practice is therefore $(1-w_x c_m f'_m P_{rm})(P-a^2P^2h^2s_f) - P + a^2P^2h^2s_f$

$$= -w_x c_m f'_m P_{rm} (P-a^2P^2h^2s_f)$$

Family limitation by sibs of affected individuals (6)

A proportion P_{sm} of the parental generation at birth are normal sibs of affected individuals. Suppose a proportion w_x of these sibs is ascertained and a proportion c_i of these subsequently reduce their intended family size by a proportion f'_x. Sibs of affected individuals have a mean liability of $\frac{1}{2}h^2a$ measured from the mean of the parental generation at birth. This is therefore the approximate mean liability of the normal sibs of affected individuals. The mean liability of the offspring of two normal parents where one parent has an affected sib is $\frac{1}{2}h^2 [\frac{1}{2}h^2a] = \frac{1}{4}h^4a$. Following the

method used for practice (3) in section (5B) the proportion of the offspring of normal sibs of affected individuals who are affected is $P + \frac{1}{4}zh^4a$. Since there is no natural selection against normal individuals the reduction in disease incidence due to family limitation by normal sibs is independent of that due to existing forces. The approximate disease incidence in the offspring is $P - a^2h^2P^2s_f - P_{sm}w_x c_i f'_x (P+\frac{1}{4}zh^4a)$. Substituting for z the approximate net change in disease incidence due to the practice is

$$-w_x c_i f'_x P_{sm} P (1+\tfrac{1}{4}h^4a^2)$$

Artificial insemination for spouses of carrier males (7)

Artificial insemination for spouses of carrier males at risk (8)

These practices are not relevant for MF diseases for the same reasons as in (2) above.

Selective abortion without reproductive compensation (9) - prospective

Suppose it is possible to detect prospectively couples where the mean liability of the two individuals exceeds x''. Suppose a proportion w_x is ascertained and a proportion c_m of these practise selective abortion but without reproductive compensation. The method of calculation of the change in disease incidence is very similar to the case when there is reproductive compensation. As in the latter case the proportion of the offspring of couples not practising selective abortion who are affected is

$$P + zh^2 \frac{[-zs_f + w_x c_m (zs_f P_x - \sqrt{2}z_x]}{1-w_x c_m P_x}$$

Similarly the proportion of offspring of couples practising selective abortion who are affected and therefore aborted is $P + zh^2 [\sqrt{2}a_x - zs_f] = P[1 + \sqrt{2}aa_x h^2 - a^2 h^2 P s_f]$. Offspring of couples not practising selective abortion therefore make up a proportion $\frac{1-w_x c_m P_x [1 - P(1 + \sqrt{2}aa_x h^2 - a^2 h^2 P s_f)]}{1-w_x c_m P_x P(1 + \sqrt{2}aa_x h^2 - a^2 h^2 P s_f)}$ of all offspring.

Since P is very small this approximates to $1 - w_x c_m P_x$. Couples practising selective abortion have no affected offspring therefore the change in disease incidence is approximately the same as that when there is reproductive compensation.

The net change is approximately

$$-w_x c_m P P_x [1 + ah^2(-aPs_f + \sqrt{2}a_x)]$$

- retrospective

Suppose a proportion w_x of couples who have had an affected child is ascertained and of these a proportion c_m practise selective abortion of affected fetuses but without reproductive compensation. As above the method of calculation is similar to that when there is reproductive compensation. If P_{rm} is the proportion of affected individuals born after the first affected child in the family then with selective abortion without reproductive compensation the disease incidence is approximately $\frac{(1-w_x c_m P_{rm})(P-a^2P^2h^2s_f)}{1-w_x c_m P_{rm}(P-a^2P^2h^2s_f)} \doteq (1-w_x c_m P_{rm})(P-a^2P^2h^2s_f)$

The approximate net change in disease incidence due to the practice is therefore $-w_x c_m P_{rm}(P-a^2P^2h^2s_f)$

DISEASES OF LATER ONSET

The differences between the changes in disease incidence and gene frequency for diseases of onset age (a) and for those of onset ages (b, c) are basically the same for diseases of all modes of inheritance. All classes of disease are therefore discussed together here.

ONSET AGE (b)

The formulae for the changes are the same as those for diseases of onset age (a). However if ascertainment is retrospective the proportion of offspring born after the first affected child has been diagnosed may be quite small. This proportion rather than P_r (or P_{rm}) determines the changes in disease incidence and gene frequency.

ONSET AGE (c)

The formulae for the changes in disease incidence and gene frequency are the same as those for diseases of onset age (a) with $s_i = 0$. This is because it is assumed that individuals destined to become affected, only after they have completed their family, have normal reproductive fitness. Retrospective ascertainment of couples at risk depends on the detection of a child who is destined to become affected only much later on in adult life. It is unlikely that many such children would be ascertained and therefore the effect of this practice would be slight. Similarly the effect of family limitation by sibs of affected individuals would be small. Most of these individuals would not be ascertained until their sib actually became affected by which time many of them would have completed their family.

The proportion of carriers of the deleterious allele (in AD diseases) or of carrier males (in XR diseases) who are ascertained might be quite small unless there is a sensitive test to detect preclinical cases. This would reduce any effect of AI in AD and XR diseases and of family limitation and selective abortion in AD diseases. For MF diseases, the proportion of individuals at high liability ascertained before they have offspring, is dependent on the age at which liability to the disease can be measured.

APPENDIX 2

FAMILY SIZE DISTRIBUTION

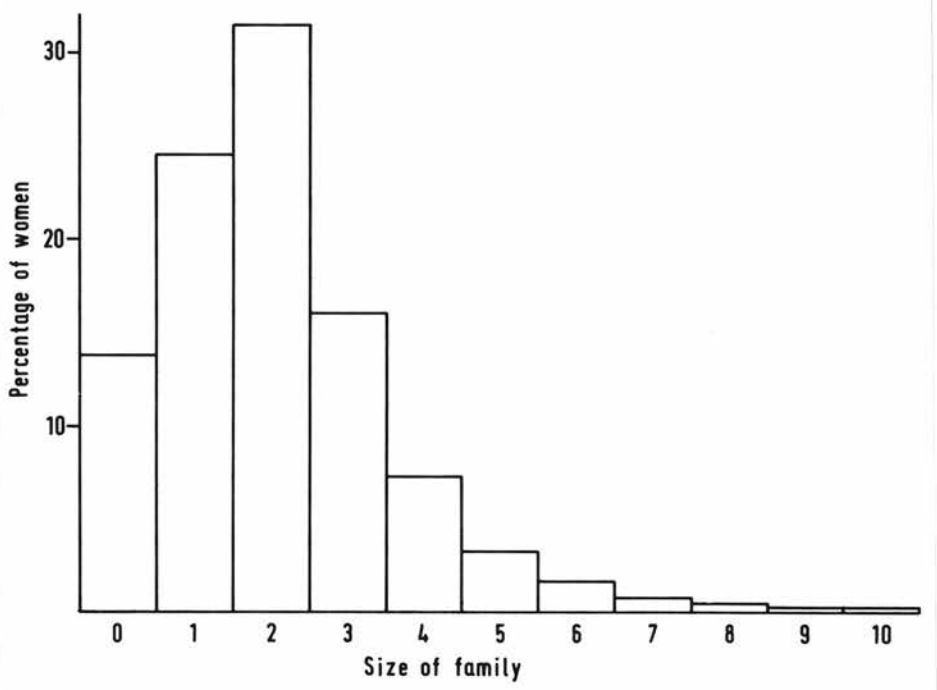
Figures from the British 1961 Census can be used to obtain an estimate of the distribution of completed family size. From Table 11(i) of the Summary Tables of the Census the proportions of married women having families of different sizes were calculated for women of seven age groups. These were, less than 20, 20-24, 25-29 ..... 40-44 and 45-49. The proportions for the last four groups did not differ significantly from each other so the figures for women aged 30-49 were pooled to obtain estimates of the values of F_s (the frequency of families of size s in the population). The values obtained are tabulated in Table A2.1 and shown in the histogram (Figure A2.1).

Table A2.1

Proportions of married women aged 30-49 having families of various sizes.

Family size	Proportion of women (F_s)
0	0.1382
1	0.2457
2	0.3147
3	0.1614
4	0.0729
5	0.0332
6	0.0164
7	0.0082
8	0.0044
9	0.0023
$\geqslant$10	0.0026

Figure A2.1 Percentage of married women aged 30-49 by size of family.


30
20
10
Percentage of women
0
1
2
3
4
5
6
7
8
9
10
Size of family

APPENDIX 3

AUTOSOMAL RECESSIVE DISEASES WITH HETEROZYGOTE ADVANTAGE

In this appendix formulae are given for changes in disease incidence and gene frequency for AR diseases with heterozygote advantage. The method of derivation is very similar to that for diseases where there is no heterozygote advantage and so only a brief outline of the method is shown here. The complete set of formulae is given in Table A3.1. As an example of a disease in a population where there is heterozygote advantage possible changes have been calculated for sickle cell anaemia in African populations. The results are plotted in Figures A3.1 and A3.2.

Method of derivation

Assume as in section (5) that the genotypes have Hardy-Weinberg frequencies at birth. Let the coefficients of selection against normal and affected homozygotes be s_{AA} and s_{aa} respectively. This is summarised below.

	AA	Aa	aa
Frequency at birth	p^2	$2pq$	q^2
Fitness	$1-s_{AA}$	1	$1-s_{aa}$

If there is random mating the mating types have frequencies and fitnesses as follows:-

Mating type	Frequency	Fitness	Proportions of offspring		
			AA	Aa	aa
AA x AA	p^4	$(1-s_{AA})^2$	1	0	0
AA x Aa	$4p^3q$	$(1-s_{AA})$	$\frac{1}{2}$	$\frac{1}{2}$	0
Aa x Aa	$4p^2q^2$	1	$\frac{1}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
AA x aa	$2p^2q^2$	$(1-s_{AA})(1-s_{aa})$	0	1	0
Aa x aa	$4pq^3$	$(1-s_{aa})$	0	$\frac{1}{2}$	$\frac{1}{2}$
aa x aa	q^4	$(1-s_{aa})^2$	0	0	1

(i) Disease incidence The approximate incidence of aa individuals amongst the offspring is

$$\frac{p^2q^2 + 2pq^3(1-s_{aa}) + q^4(1-s_{aa})^2}{(1-s_{AA}p^2 - s_{aa}q^2)^2} \doteq \frac{q^2(1-s_{aa}q)^2}{(1-s_{AA}p^2)^2}$$

The change in disease incidence between parental and offspring generations due to natural selection is therefore approximately

$$\frac{-2q^2(s_{aa}q - s_{AA}p^2)}{(1-s_{AA}p^2)^2}$$

(ii) Gene frequency The frequency of a in the parental generation at reproduction is approximately $\frac{q-s_{aa}q^2}{(1-s_{AA}p^2)}$

After selection the frequency of a in the offspring generation at reproduction is approximately

$$\frac{q^2(1-s_{aa})(1-s_{aa}q)^2 + pq(1-s_{AA}p)(1-s_{aa}q)}{1-3s_{AA}p^2}$$

The change in gene frequency between parental and offspring generations due to natural selection is therefore approximately

TABLE A3.1

Possible changes in disease incidence and gene frequency in autosomal recessive diseases where there is heterozygote advantage

Practice	Net change in disease incidence	Net change in gene frequency
(A) Dysgenic practices		
1. Improved treatment	$\frac{2q^3 s'_{aa}}{(1-s_{AA}p^2)^2}$	$\frac{pq^2 s'_{aa}}{(1-3s_{AA}p^2)(1-s_{AA}p^2)}$
2. Selection of mate	$\frac{-p^2q^2 w_{Aa} c_i (2-w_{Aa} c_i)}{(1-s_{AA}p^2)^2}$	$\frac{p^2q^2 w_{Aa} c_i (2-w_{Aa} c_i)(s_{aa}-2s_{AA})}{(1-3s_{AA}p^2)}$
3. Selective abortion with reproductive compensation - prospective	$\frac{-p^2q^2 w_m c_m}{(1-s_{AA}p^2)^2}$	$\frac{p^2q^2 w_m c_m (s_{aa}-\frac{2}{3})}{(1-3s_{AA}p^2)}$
- retrospective	$\frac{-p^2q^2 w_m c_m p_r}{(1-s_{AA}p^2)^2}$	$\frac{p^2q^2 w_m c_m p_r (s_{aa}-\frac{2}{3})}{(1-3s_{AA}p^2)}$
(B) Eugenic practices		
4. Family limitation by carriers	$\frac{-p^2q^2 w_{Aa} c_i f'_{Aa} (2-w_{Aa} c_i f'_{Aa})}{(1-s_{AA}p^2-2pqw_{Aa} c_i f'_{Aa})^2}$	$\frac{-p^3q(1-s_{AA}) w_{Aa} c_i f'_{Aa}}{[(1-s_{AA}p^2-2pqw_{Aa} c_i f'_{Aa})^2 - s_{AA}p^2]}$
5. Family limitation by carriers at risk - prospective	$\frac{-p^2q^2 w_m c_m f'_m}{(1-s_{AA}p^2)^2}$	$\frac{-p^2q^2 w_m c_m f'_m (2-s_{aa})}{(1-3s_{AA}p^2)}$
- retrospective	$\frac{-p^2q^2 w_m c_m f'_m p_r}{(1-s_{AA}p^2)2}$	$\frac{-p^2q^2 w_m c_m f'_m p_r (2-s_{aa})}{(1-3s_{AA}p^2)}$

$$\frac{pq(2s_{AA}p - s_{AA}p^2 - s_{aa}q)}{(1-3s_{AA}p^2)(1-s_{AA}p^2)}$$

Similarly changes in disease incidence and gene frequency can be calculated for the various practices studied and the above changes subtracted to obtain the net effect of a particular practice. The results are given in Table A3.1.

Sickle cell anaemia in Africa

Falconer (1960) has calculated that in parts of Africa the frequency of the sickle cell gene is about 0.2 and that the coefficients of selection against normal and affected homozygotes are approximately 0.2 and 0.75. Possible net changes in disease incidence and gene frequency can be calculated by substituting $p = 0.8$, $q = 0.2$, $s_{AA} = 0.2$ and $s_{aa} = 0.75$ into the formulae in Table A3.1. The results are plotted in Figures A3.1 and A3.2 and are discussed in section (6).

Figure A3.1 The effect of various practices on the incidence of an autosomal recessive disease where there is heterozygote advantage e.g. sickle cell anaemia in Africa.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7, 8, 9)

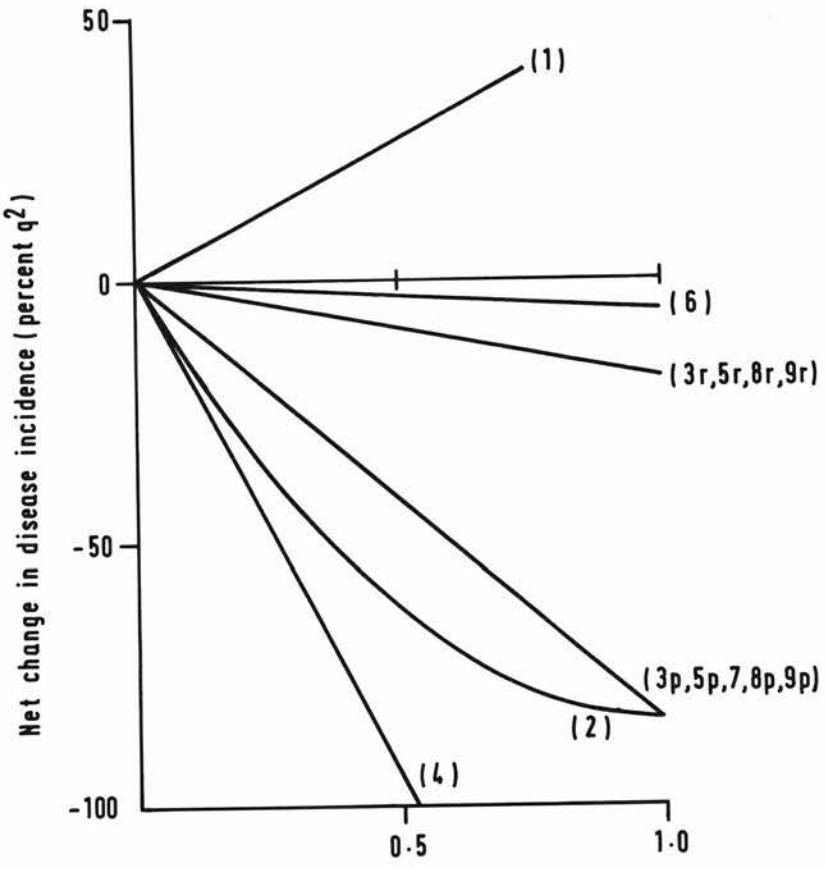

50
0
-50
-100
0·5
1·0
Net change in disease incidence (percent q^2)
(1)
(6)
(3r,5r,8r,9r)
(3p,5p,7,8p,9p)
(2)
(4)

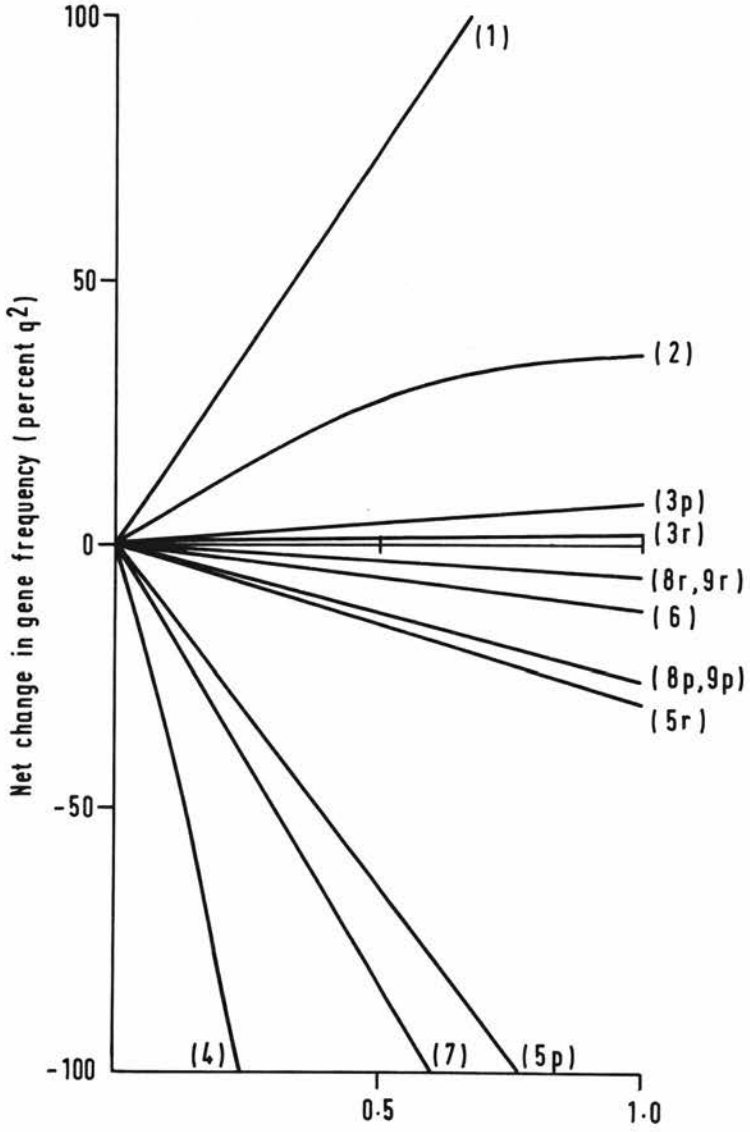
Figure A3.2 The effect of various practices on the frequency of an autosomal recessive gene where there is heterozygote advantage e.g. sickle cell anaemia in Africa.

Abscissa:-

Change in fitness of affected individuals (1)

Proportionate reduction in fertility (4, 5, 6)

Proportion adopting practice (2, 3, 7, 8, 9)


100
50
0
-50
-100
0·5
1·0
Net change in gene frequency (percent q^2)
(1)
(2)
(3p)
(3r)
(8r,9r)
(6)
(8p,9p)
(5r)
(4)
(7)
(5p)

APPENDIX 4

THE JOINT EFFECT OF IMPROVED TREATMENT AND OTHER PRACTICES ON THE FREQUENCY OF AR AND XR GENES

The joint effect on gene frequency of improved treatment and one or more of the other practices is not simply the sum of the individual effects. This is because the other practices cause a reduction in the number of affected individuals born and hence there are fewer individuals who can benefit from the treatment. The joint effect can however easily be calculated using the formulae derived in section (5) and appendix (1). The change resulting from improved treatment is calculated for the particular value of s'_i. This is then added to the changes calculated for the other practices when s_i is replaced by $(s_i - s'_i)$ in the formulae.

For example for <u>AR diseases</u> the joint effect of an increase in the fitness of affected individuals and a simultaneous voluntary reduction in the fertility of heterozygous ~~carriers~~ couples would be a change in gene frequency of $q^2 s'_{aa} - q^2 w_m c_m f'_m (2 - s_{aa} + s'_{aa})$.

If $s_{aa} = 0.9$ as in section (6) there would be no net change in gene frequency if $w_m c_m f'_m = \dfrac{s'_{aa}}{1.1 + s'_{aa}}$

Substituting in the above formula it can be calculated that if $s'_{aa} = 0.9$ (affected individuals have normal fitness) there would have to be a 45 percent reduction in the fertility of heterozygous ~~carriers~~ couples to prevent an increase in gene frequency. If $s'_{aa} = 0.1$ only a 9 percent reduction in fertility would be required. As an example for <u>XR diseases</u> consider the effect on gene frequency of improved treatment and selective abortion of affected male fetuses without reproductive compensation.

The joint effect is given by $\frac{1}{3}qs'_a - \frac{1}{3}qw_m c_m (1-s_a+s'_a)$

If $s_a = 0.9$ there would be no net change in gene frequency if

$$w_m c_m = \frac{s'_a}{0.1 + s'_a}$$

If $s'_a = 0.9$ there would be an increase in gene frequency unless about 90 percent of carrier females selectively aborted affected male fetuses.

If $s'_a = 0.1$ the corresponding value would be 50 percent.

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I declare that this thesis is my own composition and that the work herein has been carried out by myself.

INDIVIDUALS AT RISK IN FAMILIES WITH GENETIC DISEASE

BY

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Individuals at Risk in Families with Genetic Disease

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With the control of many infectious diseases and improvement in medical care, there have been dramatic changes in the pattern of mortality and morbidity in society. As a result, genetic diseases have been increased in their relative importance in the population. For example, Roberts, Chavez, and Court (1970) have found in hospital deaths among children that genetic conditions were directly or indirectly involved in over 40% of cases. Since the liability to genetic disease is inherited and intrinsic to the individual and to his family, rather than acquired or extrinsic as for non-genetic diseases, quite different systems of prevention and control are required. To some extent, these systems will require new departures from the established methods of medical practice.

Until recently the main application of medical genetics has been in counselling the parents of affected children. The possibility of extending the scope for application has been examined recently. Fraser and Motulsky (1968) estimated what proportion of cases of genetic disease might be prevented, and Smith (1970) has examined the value of different routes of prevention and the possibility of a genetic register system. McKusick (1969) has also discussed a medical record system for family follow-up in the detection and early treatment of cases of genetic disease. In a previous study (Emery and Smith, 1970), it was shown that only a small proportion of individuals 'at risk' of having affected children were in fact referred specifically for genetic counselling. Many were referred only after the birth of an affected child which otherwise could have been prevented. These results confirmed the need for a genetic register system in preventing genetic disease.

The object of this paper is to outline our experiences in recording and storing relevant data on families with genetic disease and in assessing risks to various members of the family. Details of the procedure used and a summary and interpretation of the data collected so far are presented.

Methods and Material

Assessment of Risks. Roberts (1962) grouped genetic diseases into those with a high risk of recurrence (greater than 1 in 10) and those with a low risk of recurrence (less than 1 in 20). This convention is now generally accepted and is adopted here. Thus, an individual was defined to be 'at risk' if he had a greater than 10% risk (1) of becoming affected or (2) of having affected children or children who will be 'at risk'. Those unlikely to have children in the future either due to their disease condition or due to their age (over 40 years) are excluded from category 2.

The methods of assessing the risks to family members are best described from some examples (Fig. 1).

In family A with an autosomal recessive (AR) condition, the mother was the first contact. She came for counselling *retrospectively*, ie, after the birth of her

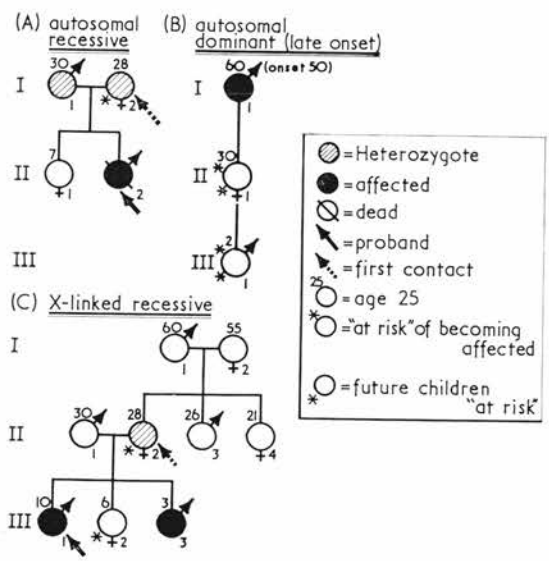

FIG. 1. Pedigrees illustrating the methods of assessing risks (see text).

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affected son, the proband. The risk of the next child being affected is high (25%) and this risk is allocated to the mother. There are no others at risk in the family.

In family B, suppose the autosomal dominant (AD) condition is Huntington's chorea. From a cumulative graph by onset age of cases of this disease (Emery, 1969), the risks of becoming affected are about 40% for the mother and 20% for the son; the risks of having children with the abnormal gene are then 20% and 10% respectively, so both are deemed to be also at risk of having children who may become affected. Since the mother (II.1) has been known to be at risk since her father's diagnosis some 10 years ago the birth of her 'at risk' son could have been prevented.

A more complex case (family C) is illustrated for an X-linked recessive (XR) condition, eg, Duchenne muscular dystrophy. With two affected sons, the mother is a definite carrier. The risks of her next having an affected boy or carrier daughter are each 25%. These risks have been summed in the XR conditions so that the combined risk in this case is taken as 50%. Similarly the daughter (III.2) is taken to be at risk since she has a 50% chance of being a carrier. Assuming the proband was diagnosed early, the birth of his affected brother (III.3) might have been prevented. Is the contact's sister (II.4) at risk? The probability that the grandmother (I.2) is a carrier is 33%, so the sister (II.4) has a 17% chance of being a carrier. Her risk of having an affected son *or* a carrier daughter is thus 18%. Further information on her carrier status could be obtained by a serum creatine kinase test (eg, Fig. 2) leading to a more precise estimate of her risk (see Emery, 1969).

Material. The families studied were from either the Edinburgh or the Manchester region during 1965–70. Many of the families were referred for genetic counselling, but some were seen for other reasons: diagnosis, teaching purposes, or research work. Some of the families were traced from hospital or health department records or through members of certain societies (eg, Muscular Dystrophy Group). The kinds and frequency of the diseases studied thus reflect the work and interests of this Department rather than the spectrum of genetic disease in the population. No attempt was made to ascertain all cases of genetic disease in a region so that this is essentially a study of ascertained families rather than a population study.

Details about the family were usually obtained from the first person to be seen in the family, the first contact. This verbal report about the pedigree and the ages and disease status of family members provided most of the information on which the following analyses are based. To systematize the form of information collected, a special record card was designed (Fig. 2) and this was used for coding and punching the data on punch cards. Details on name, address, general practitioner, etc were recorded. At examination the clinician gave a summary of the clinical report and findings, filled in other relevant details and circled the appropriate responses. Each family was allocated a separate family number. Separate cards were completed for any further members of the family who were judged to be at risk. A special two-part disease code was developed but, to conform with common usage, the International Disease Classification (with an additional 5th digit to allow for discrimination between different genetic conditions) will be used in future. A second disease category was available, to record associations of different diseases in one family. The remainder of the first side of the card dealt with details on sex, dates of birth, details of the visit, and the mode of referral.

On the reverse side of the card (Fig. 2 below), the pedigree and further details were recorded as shown.

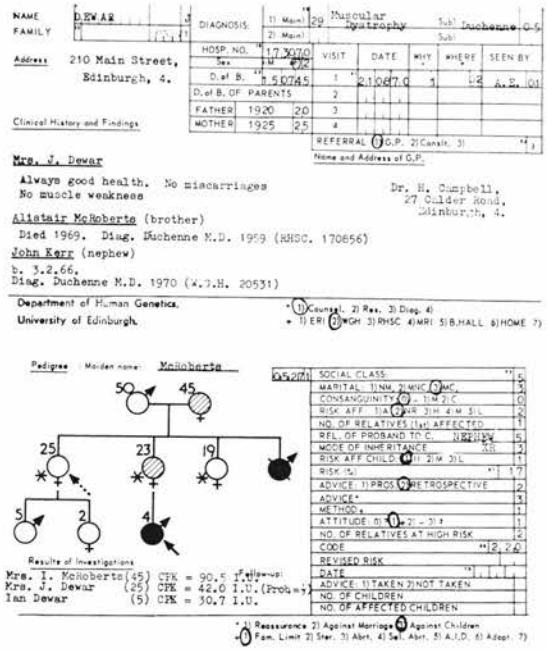

FIG. 2. Example of a completed family record card. The details are purely fictitious and are used only for illustration.

These included social class (5 groups); marital status (not married, married with no children, married with children); consanguinity (none, mild, close); status (affected, no risk, high risk, medium risk, low risk); number of first-degree relatives affected; relationship of the proband; mode of inheritance; risk of having an affected child (high, medium, low—and as a percentage); and whether the record was made before (prospective) or after (retrospective) the birth of an affected or 'at risk' child to the individual concerned.

If the person was counselled, the advice given was noted, together with any method of family limitation advised and the person's attitude to the counselling. Finally, for the first contact in the family, the number and relationship codes of relatives at risk were recorded.

Further columns were left for any revision of the risks and for details of follow-up.

The information obtained on the families was not always complete because the cards for relatives at risk were prepared from the information given by the first contact at interview. Moreover some of the families were ascertained before the present recording scheme was developed, so past files had to be used and these were often incomplete. This may have led to some underestimation of the numbers affected and at risk, for only recorded information could be used. For analysis on a particular topic all data available on that topic were used. Almost all families ascertained were included in the analysis. These included conditions that were either not serious or not genetic or whose nature was not resolved, and form the 'other' category in Table I. The term 'multifactorial inheritance' in Table I refers to familial diseases which are possibly due to many loci plus the effects of environment and include some of the congenital malformations, diabetes mellitus, and schizophrenia (Carter, 1969).

Results

Families. Reasons for ascertainment and other details about the families studied are given in the series of histograms in Fig. 3. Over half of the families were referred for genetic counselling and the rest mainly for diagnosis or research. The chief source of families referred was the hospital consultant who contributed almost two thirds of the total. Most of the remainder were referred directly by the family's general practitioner. The distribution of the families by social class, though not directly comparable to the distribution in the

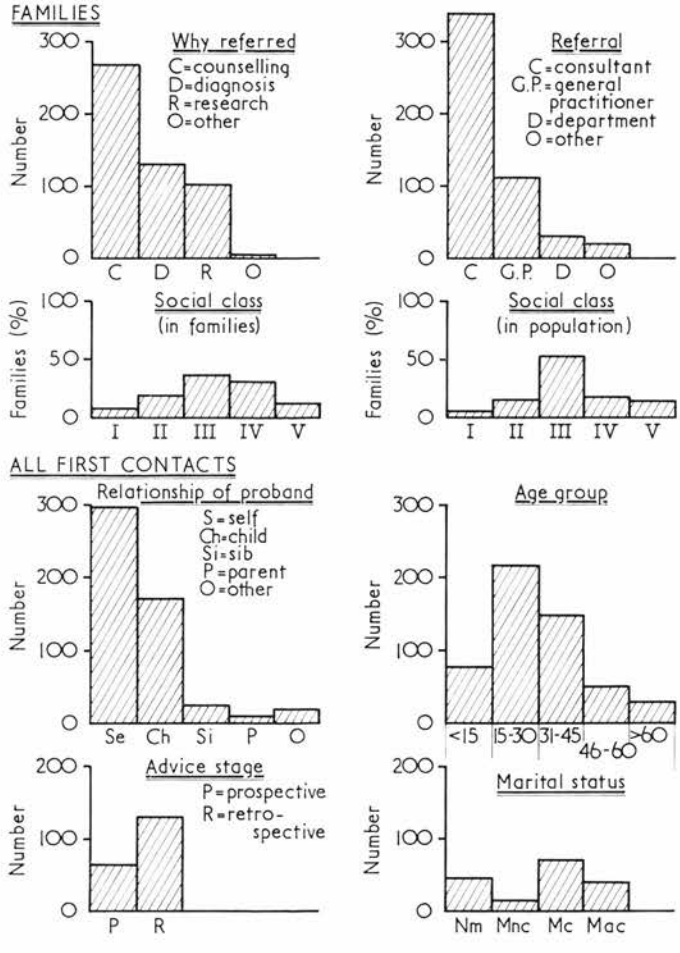

FIG. 3. Distributions of families and of first contacts (for serious genetic conditions) by various classifications of the data.

population (1961 Census) because of age and other differences, shows an apparent excess of families in social classes 1 and 4 and a corresponding deficit in class 3. However all social classes are well represented in the families ascertained.

First Contacts. The remaining histograms in Fig. 3 refer specifically to the first contact in each family. Most of these were either the affected proband (usually in families referred for diagnosis or research) or the proband was the child of the first contact (usually in families referred for genetic counselling). This indicated that few other relatives in affected families were referred about their possible risk (*cf*, Fig. 6). The age distribution of first contacts shows that they were largely in the reproductive age groups. This reflects concern about their risks of having affected children and about affected children born. Two thirds of the contacts at risk of having affected children were seen retrospectively, that is after the birth of an affected or at risk child. Among first contacts who were married and at risk of having affected children, almost 40% had no children (MNC) or had only affected children (MAC) so far. Genetic counselling was thus very relevant to them at this stage in their family life.

Risks and Mode of Inheritance. A tabulation by mode of inheritance of the numbers affected and the numbers at risk is given in Table I. In some 114 of the families recorded, the disease was not serious or judged to be not genetic. No further persons in these families were considered to be at risk. Among the families with chromosomal abnormalities or with multifactorial inherited conditions, there were relatively few persons at risk. By contrast, for diseases inherited in a simple Mendelian manner, a high proportion of the families had persons at risk; autosomal dominant (AD) 90%, autosomal recessive (AR) 53%, X-linked recessive (XR) 84%. This confirms theoretical calculations (Smith, 1970) that preventive methods will be most effective for the simply inherited genetic diseases.

The numbers affected reflect the burden of the genetic conditions on these families. There was an average of over three persons affected per family for the AD conditions, two persons for the XR conditions, and about 1·5 persons for the AR and multifactorial conditions. Moreover, the burden to the family is a continuing one in that a high proportion (over two thirds) of the affected persons are still alive.

The future prospects for these families are also serious because many have further members at risk either of becoming affected themselves or of having affected children. The distribution of the numbers at risk is shown in Fig. 4. Half the families with persons at risk had more than one member at risk and some families had many members at risk. In Table I, the three categories listed under 'number at risk' are mutually exclusive so their total indicates the total number at risk in these families. This averages 4·0 persons for AD conditions, 3·5 persons

TABLE I

MODE OF INHERITANCE OF NUMBERS AFFECTED AND NUMBERS AT RISK IN 559 FAMILIES ASCERTAINED

	Serious Genetic Conditions					Others*
	Mode of Inheritance					
	Autosomal Dominant	Autosomal Recessive	X-linked Recessive†	Multi-factorial	Chromo-somal	
Families						
Number	124	112	102	78	29	114
Number with someone at risk‡	111	59	86	18	2	0
Persons						
Number affected						
All	361	157	198	113	32	90
Alive	255	119	137	68	24	72
Number at risk						
Only of becoming affected	39	5	15	4	0	0
Both of becoming affected and of having affected children**	239	0	15	2	0	0
Only of having affected children**,††	158	54	272	16	2	0
Births since 1960 at risk a priori						
Number of children						
Affected	23	14	21	3	0	0
At risk††	77	2	77	3	0	0
Not at risk	8	15	12	1	0	0

* Not serious, not resolved, not genetic. † 93 Families with muscular dystrophy. ‡ Risk 10% or higher. ** Persons under age 40. †† Includes carrier daughters in X-linked disorders. (For other details see text.)

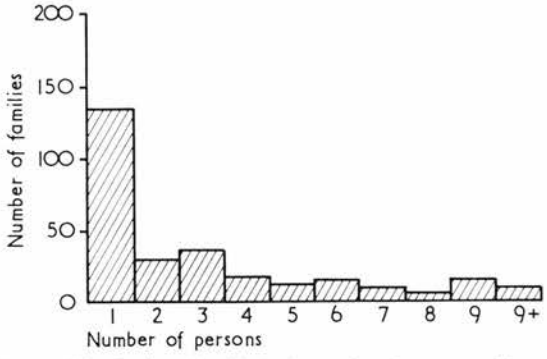

FIG. 4. Distribution of families by the number of persons at risk.

for XR conditions, and about one person for AR and multifactorial conditions.

Individuals at Risk. People at risk of becoming affected were largely in families with AD conditions with late onset (Table I), where a parent becomes affected after his children (and even grandchildren) have been born. With increasing age the risks to the children (if still unaffected), and to the grandchildren, will gradually fall. These patterns are reflected in the distribution by age of the numbers at risk of becoming affected (Fig. 5).

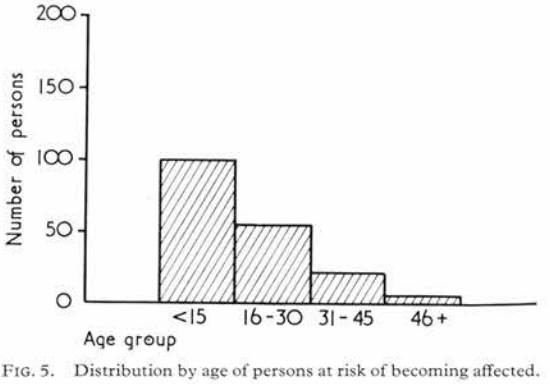

FIG. 5. Distribution by age of persons at risk of becoming affected.

For individuals at risk of having affected children or children at risk, all three simple modes of inheritance (AD, AR, and XR) were involved, although the AD-inherited conditions again predominated. The distribution of risks by age is given in Table II. The risks fall naturally into 3 groups; at about 50%, at around 25%, and from 10 to 19%. The latter group represent only 14% of all at risk, so it is the higher risk categories which predominate. The distribution of the risks also changes with age ($\chi^2 = 35$, $p < 0{\cdot}001$) with the proportion in the highest risk category increasing with age. This was largely because such high risks occur firstly, in AD conditions when the person is diagnosed as affected and onset is often late and secondly, in XR conditions when a mother is proven to be a carrier after the birth of an affected son.

TABLE II

NUMBERS, BY AGE AND RISK, OF PERSONS AT RISK OF HAVING AFFECTED CHILDREN

Age (yr)	Percentage Risk		
	10–19%	20–29%	over 30%
Under 16	29	122	41
16–30	36	94	98
31–40	19	44	60

The distribution by relationship of the proband to those at risk in the family is given in Fig. 6. There is a strong contrast with the equivalent distribution for first contacts (Fig. 3). This demonstrates that many kinds of relatives who are at high risk are not being ascertained or counselled by normal medical practice.

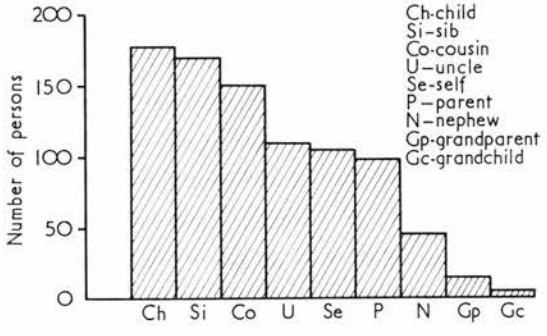

FIG. 6. Distribution of persons at risk of having affected children, by relationship of the proband.

Births at Risk *a priori*. The results for children born since 1960 to parents who where at risk *a priori* of having affected children confirm the risks involved. Of 256 births in this category, some 61 (24%) of the children were affected while a further 159 (61%), though normal so far, are still at risk of becoming affected themselves or of having affected children.

Discussion

In this department a genetic register system is being developed and is referred to by the acronym 'RAPID' (Register for the Ascertainment and Prevention of Inherited Disease). Here we report results for the initial stage of development of the register, using some 559 ascertained families. The objectives in this stage were (1) to gain experience in recording and handling family data and in assessing risks to family members and (2) to examine the need and scope for a preventive system in practice. Our results clearly show the area where preventive effort can be best applied and justify the implementation of a genetic register system in practice.

The main scope for preventing genetic disease lies, at present, with the simply inherited diseases despite the fact that other diseases are much more frequent in the population. This is because the proportion of individuals at risk is greater, and the risks are higher in families with simply inherited conditions than in families with multifactorial or chromosomal disorders. Thus it is proposed that preventive effort should be largely restricted, at least initially, to the simply inherited conditions. Thus we have defined a discrete problem area which should give worthwhile returns for any resources committed. However, it should be emphasized that even for the simply inherited disorders, it will be possible to prevent only a proportion of cases, since some will occur in families which have not been ascertained previously (Smith, 1970).

In the 338 families with simply inherited conditions, there were some 716 affected individuals, of whom 511 are still alive. This emphasizes the past and continuing burdens on these families and their need for medical care and supervision. Moreover, and perhaps more disconcerting, is the fact that the burden in these families is likely to increase in that there are some 797 individuals still at risk, either of becoming affected themselves or of having children who may be affected. This shows the need for genetic counselling and supervision to be extended to all family members at risk (Fig. 6), rather than only to the first contact in the family. That is, the initiative in prevention should be undertaken as a health service, rather than left to the individual who may be unaware of his risk. This point was stressed in a previous study (Emery and Smith, 1970) where it was shown that only a small proportion (14%) of those at risk was referred for genetic counselling. There is at present no defined procedure or responsibility for tracing and counselling individuals known to be at risk. Herein lies the value of a genetic register system.

The development of the RAPID system is now proceeding in several areas. One is to follow-up individuals who have been counselled, to keep in touch with the family, and to assess the value of the counselling methods in preventing genetic disease. Another is to develop procedures for contacting and counselling others at risk in the family, working always through the general practitioner of the person concerned. To extend the system to a population basis, methods and sources for ascertaining families with simply inherited genetic disease are being examined. Through linkage with hospital, GP, health department, and other records, relevant families will be screened for investigation and counselling. The data storage and handling operations are being organized around a computer, and much of the system software has been written. The procedures include data vetting, monitoring, listing, updating, scheduling for follow-up, and other items. Several hurdles are foreseen. Among them are the geographical dispersion of family members, security of data on file, the privacy of the individual, the attitude of healthy individuals to possible genetic risks, the effectiveness of counselling, and the organizational details required to make the register an effective preventive system.

Summary

This report concerns data on 559 families with genetic disease referred for genetic counselling, diagnosis or research. It summarizes our work on the initial stages in the development of a genetic register system (RAPID) for the ascertainment and prevention of genetic disease. The procedures for assessing risks to individuals in ascertained families are described, and methods of recording and handling the relevant family records and details on individuals 'at risk' are also shown.

Data are presented on reasons and routes of referral and on social class of the families ascertained and on the age, marital status, risk etc of individuals referred. In the 559 families studied there were 951 affected individuals (of whom 70% were still alive) and some 821 individuals who were judged to be at risk themselves or at risk of having affected children. The analyses confirm the need for a genetic register system in practice and show that the simply inherited genetic diseases offer the best scope in prevention.

We would like to thank Mrs E. R. Clack and Miss M. S. Watt, SRN for their help in tracing families. This

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Equilibrium Frequencies in X-linked Recessive Disease

SUSAN M. HOLLOWAY[1] AND CHARLES SMITH[1]

Haldane's [1] formula for the equilibrium frequency of rare X-linked recessive diseases maintained by mutation can be extended to cover a wide variety of situations in genetic counseling, antenatal diagnosis, and eugenic consequences of different medical practices. Some of these have been considered already [2–4] but the studies have dealt with the effects of changing one factor at a time. In this paper, formulas are developed so that the net effect of any combined set of factors can be considered, in order to study the balance among different factors and their combined equilibria. The initial sections of the paper introduce the form of the procedure for simple cases; then the methods are generalized to take into account several variables concurrently. Finally, the use of the formulas is illustrated and discussed.

SIMPLE EQUILIBRIA

To introduce the methods and notation used (see Appendix), simple cases dealing with survival rates of affected males and reproductive practices of affected males and carrier females are considered. Let M and F be the equilibrium frequencies at birth of affected males and carrier females, respectively. Let the relative reproductive fitness (number of offspring born relative to the number of offspring born from normal individuals) of affected males and of carrier females be m and f, respectively. Note that this deals with the actual or achieved fertility, rather than with the potential fertility, genetic or otherwise.

Affected males are either the result of a new mutation or are the offspring of carrier females (half of whose sons are affected). Then, if μ is the mutation rate per gamete,

$$M = \mu + Ff/2. \tag{1}$$

Similarly, carrier females can arise by a new mutation (in either gamete), from carrier mothers (half their daughters are carriers), or from affected males (all daughters are carriers), so

$$F = 2\mu + Ff/2 + Mm. \tag{2}$$

The equilibrium frequencies can then be found, in terms of the mutation rate (μ), by substituting equation (1) in (2) and solving for F, giving

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$$F = \frac{\mu(2 + m)}{[1 - (f/2)(1 + m)]}, \tag{3}$$

and similarly for M.

These formulas can deal with changes in the fitness of affected males and carrier females as a result of genetic counseling or through improved treatment or survival of affected males. For example, if the fitness of affected males became 0.5 and that of carrier females was 0.8, then from equations (1) and (3) the equilibrium frequencies of affected males and carrier females would be 3.5 μ and 6.3 μ, respectively.

The formulas can be extended to deal with different mutation rates in males (μ_m) and females (μ_f). The contribution of mutation to M is μ_f and to F is $(\mu_m + \mu_f)$. The solution for F then becomes $[\mu_m + \mu_f(1 + m)]/[1 - (f/2)(1 + m)]$, and similarly for M.

COMPLEX EQUILIBRIA

In practice, many other factors are likely to affect the net reproductive fitness of affected males and carrier females, so that the equilibrium frequency will usually be a complex function of several factors. Each of these will first be considered separately. Then the joint effect of the different factors will be considered, and general expressions from which the complex equilibria can be calculated will be derived.

Stage of Detection

If there is a previous family history of a disease or if carrier tests are available, carriers may be detected before any affected offspring are born. Following Fraser [2], this will be called prospective detection. However, most carriers of X-linked conditions will be detected only after the birth (or diagnosis) of an affected son; that is, detection is retrospective. Note that a proportion of carrier females will remain undetected since they have no affected offspring.

Among all carriers not detected prospectively, the proportion of cases born (or preventable) after the first case can be derived as follows. With family size n, an average of $n/4$ affected sons is expected. In a proportion $(3/4)^n$ of families of carrier females, there will be no affected sons. In the remainder $[1 - (3/4)^n]$, there will be at least one affected son, the first case in the family. Thus, the proportion of first cases among all cases in families of size n from carrier females is

$$z_n = [1 - (3/4)^n]/(n/4), \tag{4}$$

as shown by Fraser [5]. Table 1 illustrates this result for families of size three. The proportion of first cases among all affected is 37/48, which is equal to z_n for $n = 3$. The proportion of cases born after the first case is, of course, $(1 - z_n)$.

Since z_n is dependent on family size (n), the distribution of family size in the population must be taken into account. Fraser [5] has evaluated the weighted mean value $(\bar{z})$ for different distributions of family size. For example, for a Poisson

TABLE 1

PROPORTION OF FIRST CASES IN FAMILIES OF SIZE THREE

Family Order 1-2-3	Frequency (× 64)	No. First Cases	No. Affected	No. Normal Born before First Case	Total Normal Born
*NNN**	27	0	0	3	3
NNA	9	1	1	2	2
NAN	9	1	1	1	2
ANN	9	1	1	0	2
NAA	3	1	2	1	1
ANA	3	1	2	0	1
AAN	3	1	2	0	1
AAA	1	1	3	0	0
Total	64	37	48	111	144

* N = normal; A = affected.

distribution with mean family sizes of two and three, the proportions of first cases among all cases are 79% and 70%, respectively. With the negative binomial, the other distribution commonly used to describe distribution of family size, the figures are somewhat higher [5].

It can be shown that $\bar{z}$ also measures the proportion of normal individuals born before the first case. For example, in table 1 this proportion is 111/144. The quantity $\bar{z}$ also gives the average fitness of carrier females if they have no further children after the first case in their family.

Reproductive Fitness

The relative fitness of carrier females will depend on their reproductive practices after detection. Some may terminate their family, others may have normal family size, and still others may compensate for the birth of affected children. A proportion of all carrier females in the population will not be detected, and these are assumed to have normal family size. This group is included implicitly in all the results derived below.

Carrier females who are detected prospectively may have no children and will have a zero fitness. Any who partially restrict their family after detection will have a fitness of less than one, while those who go on to have their normal family size will have a fitness of one. Those terminating their families after the birth of an affected child will have a mean fitness of z.

Some carrier females may compensate for the birth of a affected children so as to have the intended number n of normal children, so-called full reproductive compensation. The total number of children born will be $(a + n)$. The ratio $a/(a + n)$ will be equal to p, the segregation ratio, so $n = a(1 - p)/p$. The mean fitness for such carrier females is then $(a + n)/n$, which is equal to $1/(1 - p)$; this result holds for any family size.

Some carrier females may wish for the intended number of living children. If a

proportion d of affected children do not survive, the total number of children born will be $(n + ad)$. By repeating the above argument, the fitness of such carrier females can be shown to be $1/(1 - dp)$.

Selective Abortion

To deal with selective abortion, the class of offspring selectively aborted must be considered. Various classes of offspring could be selectively aborted: (1) affected males, (2) all males, or (3) affected males and carrier females. Consider the reproductive fitness f^* of carrier females detected prospectively, measured in terms of number of offspring conceived (omitting natural abortions). The observed fitness f, in terms of numbers born, is then

$$f = f^*(x_{NF} + x_{NM} + x_{CF} + x_{AM})/4, \tag{5}$$

where x_{NF}, x_{NM}, x_{CF}, and x_{AM} refer, respectively, to the proportions born of normal females, normal males, carrier females, and affected males conceived. Thus the value of f^* can be derived. Similarly for affected males, female offspring (all carriers) could be selectively aborted. The observed fitness m in terms of offspring born is then

$$m = m^*(2y_{NM} + 2y_{CF})/4, \tag{6}$$

where y_{NM} and y_{CF} are the proportions born of normal males and carrier females conceived.

If the family is detected retrospectively, a proportion z of offspring will be born before detection, as shown in the previous section. The observed fitness f of carrier females in terms of offspring born then becomes

$$f = z + (f^* - z)(x_{NF} + x_{NM} + x_{CF} + x_{AM})/4. \tag{7}$$

Combined Equilibria

All the factors considered above can now be combined into a single set of formulas covering a wide range of situations and can deal with the various factors either singly or in combination.

As discussed earlier, all carrier females are unlikely to adopt the same reproductive practices after detection. To deal with this, let the subscript i refer to the ith group of carrier females who make up a proportion P_i of all carrier females. Similarly, let the subscript j and P_j refer to a particular group of affected males. The procedure then is to calculate, for each group i, the fitness f^*_i in terms of conceptions (given the observed fitness f_i in terms of births) and to weight the values according to the proportion in the group. The equilibrium frequencies can then be written as for equations (1) and (2), namely,

$$M = \mu + \frac{F}{2} \sum_i P_i[z_i + (f^*_i - z_i)x_{AM_i}]; \tag{8}$$

$$F = 2\mu + \frac{F}{2} \sum_i P_i[z_i + (f^*_i - z_i)x_{CF_i}] + M \sum_j P_j m_j y_{CF_j}. \tag{9}$$

By substituting in these formulas, the equilibrium frequencies can be easily derived. If there is no selective abortion, then $f^*_i = f_i$, and all x and $y = 1$. The formulas can be extended to deal with different mutation rates in males and females as before.

Application

To illustrate an application of the previous sections, consider a rather complex case—deriving the equilibrium frequency for an X-linked condition, say hemophilia. Affected males now tend to survive longer and may have more offspring than previously. Genetic counseling is available, and carrier tests and accurate diagnosis can be made. Selective abortion of males from carrier females and of daughters of affected males is also possible and may be used in a proportion of families.

Details of an example are given in tables 2 and 3. Among affected males, suppose 10% do not survive to reproduction, a further 20% have no offspring, and 60% have normal fitness. Suppose the final 10% of the affected males opt for selective abortion of their female offspring, half with no reproductive compensation and half with full reproductive compensation. However, since affected males do not pass X-linked genes to their sons and, using selective abortion, have no daughters, their actual fitness in this case need not be considered.

Among carrier females, those detected prospectively and those detected retrospectively must be treated separately (table 3). For prospective detection the details are similar to those for affected males. If carrier females terminate their family retrospectively, their average fitness ($\bar{z}$) will be about 70%–80%, as discussed earlier. If they use selective abortion of males but have the normal number of pregnancies, the relative fitness for conceptions (f^*) will be 1.0, and for offspring born (f) it will be 0.88. With selective abortion of males and normal family size, the fitness for numbers born (f) will be 1.0. The fitness for numbers conceived (f^*) is then given by $f = 1.0 = 0.75 + (f^* - 0.75)(1 + 1 + 0 + 0)/4$, so that f^* is 1.25. With selective abortion of males and a full family (n) of unaffected

TABLE 2

POSSIBLE REPRODUCTIVE PRACTICES FOR AFFECTED MALES SHOWING PROPORTION AND FITNESS FOR EACH TYPE

AFFECTED MALES	PROPORTION (P_j)	RELATIVE FITNESS	
		No. Born (m_j)	No. Conceived (m^*_j)
Not surviving	0.10	0	0
No offspring	0.20	0	0
Normal family size	0.60	1.0	1.0
Selective abortion of female offspring (n offspring conceived)	0.05	0.5	1.0
Selective abortion of female offspring (n offspring born)	0.05	1.0	2.0

TABLE 3

POSSIBLE REPRODUCTIVE PRACTICES FOR CARRIER FEMALES SHOWING PROPORTION AND FITNESS FOR EACH TYPE

A. DETECTION

	DETECTION OF CARRIER FEMALES	
	Prospective	Retrospective
Proportion	0.20	0.80
Proportion of offspring born before detection ($\bar{z}$)	0.0	0.75

B. REPRODUCTIVE PRACTICE

REPRODUCTIVE PRACTICE AFTER DETECTION	PROSPECTIVE PROPORTIONS (P_i)	FITNESS No. Born (f_i)	FITNESS No. Conceived (f^*_i)	RETROSPECTIVE PROPORTIONS (P_i)	FITNESS No. Born (f_i)	FITNESS No. Conceived (f^*_i)
No further offspring	0.30	0	0	0.40	0.75	0.75
Normal family size (n offspring born)	0.10	1.0	1.0	0.10	1.0	1.0
Selective abortion of males (n offspring conceived)	0.40	0.5	1.0	0.25	0.88	1.0
Selective abortion of males (n offspring born)	0.10	1.0	2.0	0.10	1.0	1.25
Selective abortion of males (n unaffected offspring born)	0.10	1.0	2.0	0.15	1.19	1.63

children, the relative fitness for offspring born (f) is equal to $1 + z/4$, since one-fourth of the children at detection will be affected, and the relative fitness for offspring conceived (f^*) is 1.63.

The values in tables 2 and 3 can be substituted directly in equations (8) and (9) to derive the equilibrium frequencies. These were found to be 3.7 μ for males and 8.4 μ for females. A computer program was written to derive the equilibrium frequencies for any set of variables studied and is available on request.

Relative Importance of Factors

One reason for trying to combine various factors affecting an equilibrium was to study their relative effects and to see where opposing forces would balance. A large variety of comparisons could be made using the above procedures, but only a few cases of special interest are considered here.

In the absence of selective abortion, the critical factor in determining the equilibria is the average fitness of carrier females, and similarly the average fitness of affected males. Thus, the combined effects of any group of fitnesses can be simply

summarized by taking the average fitness for the group and substituting in equation (3) to get the equilibrium frequency.

With selective abortion, the type of offspring born, as well as their number, must be considered. So the average fitness does not summarize the effects of the various factors, and the full procedure as summarized by equations (7), (8), and (9) must be used. The effects of selective abortion with full reproductive compensation are of special interest, for these could theoretically give rise to a continuous increase in frequency with time. However, this is unlikely in practice, for there are other factors with balancing effects. The effects of a proportion of carriers having no children after detection are considered in figure 1. As this proportion

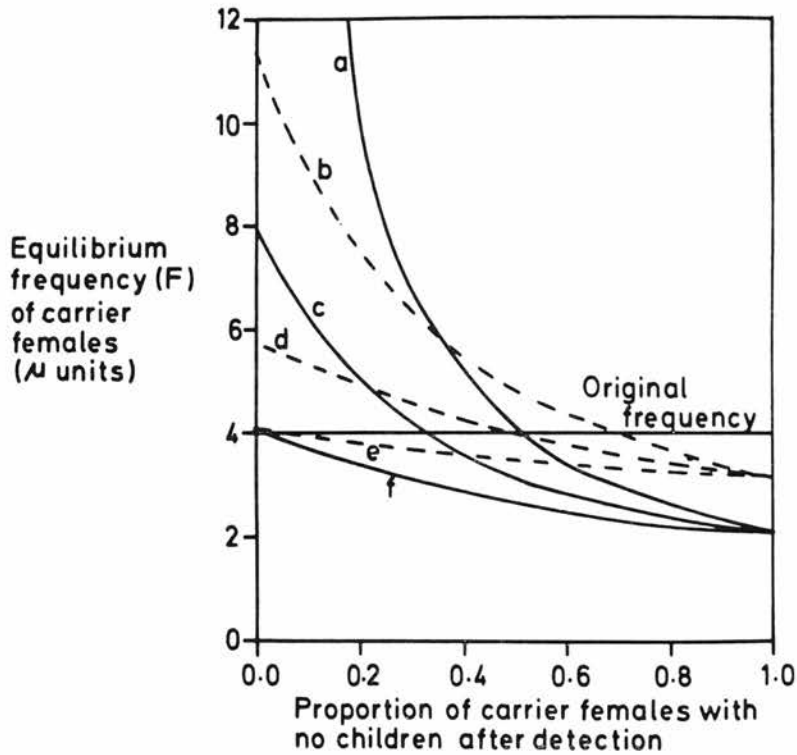

FIG. 1.—Equilibria from selective abortion of all males from carrier females following detection. (Affected males do not reproduce.) *Solid line* = prospective detection; *broken line* = retrospective detection; ($z = 0.7$).

increases the equilibrium frequency in each case falls. Case *a* shows the extreme situation with prospective detection and full reproductive compensation. If only a small proportion of detected carriers have no children, the frequency will not rise continuously but will reach a new, though elevated, equilibrium value.

With retrospective detection and full reproductive compensation (case *b*), much lower equilibrium frequencies are expected. However, a reduction in the number

of births from detected carriers will be expected in practice, since with selective abortion of males, two pregnancies are required on average for each female born. If carrier females have only their intended number of pregnancies, the equilibrium frequencies will be unchanged, or decreased if some carriers have no children after detection (cases *e* and *f*). The two other cases (fig. 1, *c* and *d*) represent intermediate situations. Case *d* refers to retrospective prevention where the intended number of offspring, including the affected proband, is produced. Case *c* represents prospective prevention where half the carriers practice full reproductive compensation and the other half have only their intended number of pregnancies. These result in only moderate increases in frequency above the original equilibrium value.

DISCUSSION

The equilibrium frequencies for X-linked diseases depend on many factors associated with survival and with reproductive practice of affected and carrier individuals. Several workers, but especially Fraser [2], have discussed the effects of changes in single factors acting in isolation, that is, assuming that other factors remain unchanged. The estimated changes in frequency have been very relevant in setting upper limits for the effect of each factor. In practice, several factors are likely to change concurrently, so that to estimate new equilibrium levels more accurately, methods to take the various factors into account are required. The methods outlined here allow combination of any set of factors in order to study and assess their combined equilibrium.

Though the theoretical derivation of equilibria is clear, their determination in practice may be more difficult because the statistics required may be difficult to estimate reliably and will vary over time and place. If the disease is rare, the numbers in various reproductive groups may be small and variable and thus contribute to unreliable estimates. The distributions of intended and completed family size will only be known in retrospect, after reproduction has ceased and may also vary with time. Similarly, the fitness of an individual cannot be measured until the end of reproductive life. These derivations also assume that the disease is caused by a single genetic entity. Both genetic heterogeneity and the existence of phenocopies are factors that would affect the equilibrium values for the frequency of the disease.

With X-linked conditions the approach to new equilibrium levels is reasonably rapid [6], reaching halfway to the new equilibrium in 3–6 generations, compared with hundreds of generations for autosomal recessive conditions. However, it is likely that survival, reproduction, detection, selective abortion, and other factors will change with time and will differ between countries, social groups, and so on. Thus, the equilibria are unlikely to be constant but will continue to vary over time and place.

SUMMARY

Formulas are developed to calculate the equilibrium frequency of X-linked diseases in complex situations. These include the combined effects of survival of

affected individuals, variable reproductive performance of affected males and carrier females, variable stages of detection, and selective abortion. The net effect of any combined set of factors on the equilibrium frequency of the disease can thus be studied.

APPENDIX

Symbols

NF, NM, CF, AM = normal females, normal males, carrier females, affected males
F = equilibrium frequency of CF born
M = equilibrium frequency of AM born
p = segregation ratio
μ = mutation rate per gamete per generation
n = family size
a = average number of AM
z = proportion of offspring born before detection of the family

Parameters Varying with Reproductive Class

P_i = proportion of CF in class (i)
P_j = proportion of AM in class (j)
f_i = relative fitness of CF in class (i) in terms of offspring born
m_j = relative fitness of AM in class (j) in terms of offspring born
f^*_i = relative fitness of CF in class (i) in terms of offspring conceived
m^*_j = relative fitness of AM in class (j) in terms of offspring conceived
x_{NF_i} = proportion of NF born among those conceived by CF in class (i) after detection
y_{NM_j} = proportion of NM born among those conceived of AM in class (j)

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ABSTRACT OF THESIS

Name of Candidate SUSAN MARY HOLLOWAY

Address .....

Degree Ph.D. *Date* September, 1974.

Title of Thesis Effects of medical and social practices on the frequency of deleterious genes in the population

Since the virtual eradication of many infectious diseases in civilised populations, diseases which are at least partially genetic have increased in their importance as the primary cause of death and morbidity. Much concern has been expressed that current and future medical practices might further increase the burden on medical services of genetic diseases by causing increases in their incidence. In this thesis a study has been made of eugenic, as well as dysgenic, effects of some of these possible practices.

Single generation changes in disease incidence and gene frequency have been calculated for practices acting alone and in combination. No attempt has been made to calculate possible effects of changes in existing forces such as mutation and natural selection. All the changes calculated are those which would result from the new practices acting alone and this makes it possible to measure the relative effects of the new forces.

Formulae for calculating possible changes have been derived for ~~AR, AD, XR and MF~~ autosomal recessive, autosomal dominant, x-linked recessive and multifactorial diseases and graphs drawn to illustrate the effects of the practices for diseases of early onset where affected individuals have low fitness. The theoretical changes calculated suggest that with the possible exception of AD diseases and AR diseases where there is heterozygote advantage the overall effect of the practices is likely to be a decrease in disease incidence in one generation. The estimated changes in gene frequency indicate that there is likely to be a longer term decrease in incidence of AR diseases but there might be an increase in incidence of AD and XR diseases.

The realisation of these theoretical changes is dependent upon the feasibility of the practices for particular diseases, the proportion of individuals ascertained and the proportion of these individuals adopting a particular practice.

Use other side if necessary.

At present the practices are only possible for a limited number of diseases but prospects seem hopeful for their extension to other diseases particularly those with AR and XR modes of inheritance. Most individuals to whom the practices would be relevant are only ascertained at a stage when their subsequent adoption of any of the practices would have a minimal effect on the overall disease incidence. There is much scope for detecting more individuals at risk by contacting relatives in families with AD and XR diseases or by screening to detect heterozygous carriers in recessive diseases. The results of the follow-up studies discussed in section (3) indicate that couples would use the new practices if they were available.

Thus it seems that with advances in medical research and the detection of more individuals at risk these theoretical changes might actually occur. However in many cases the changes might be limited by some of the factors discussed in section (10) particularly cost and availability of resources.